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VOL. 33, NO. 6 JUNE, 1960

Twenty-fifth Annual Convention
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23, 24, 25, 26 October 1960

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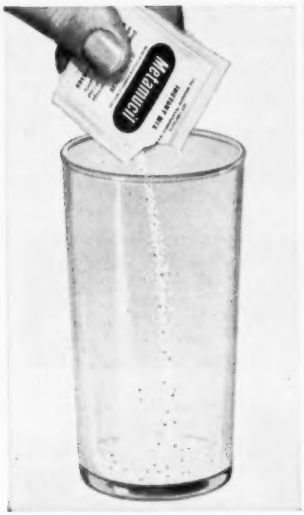

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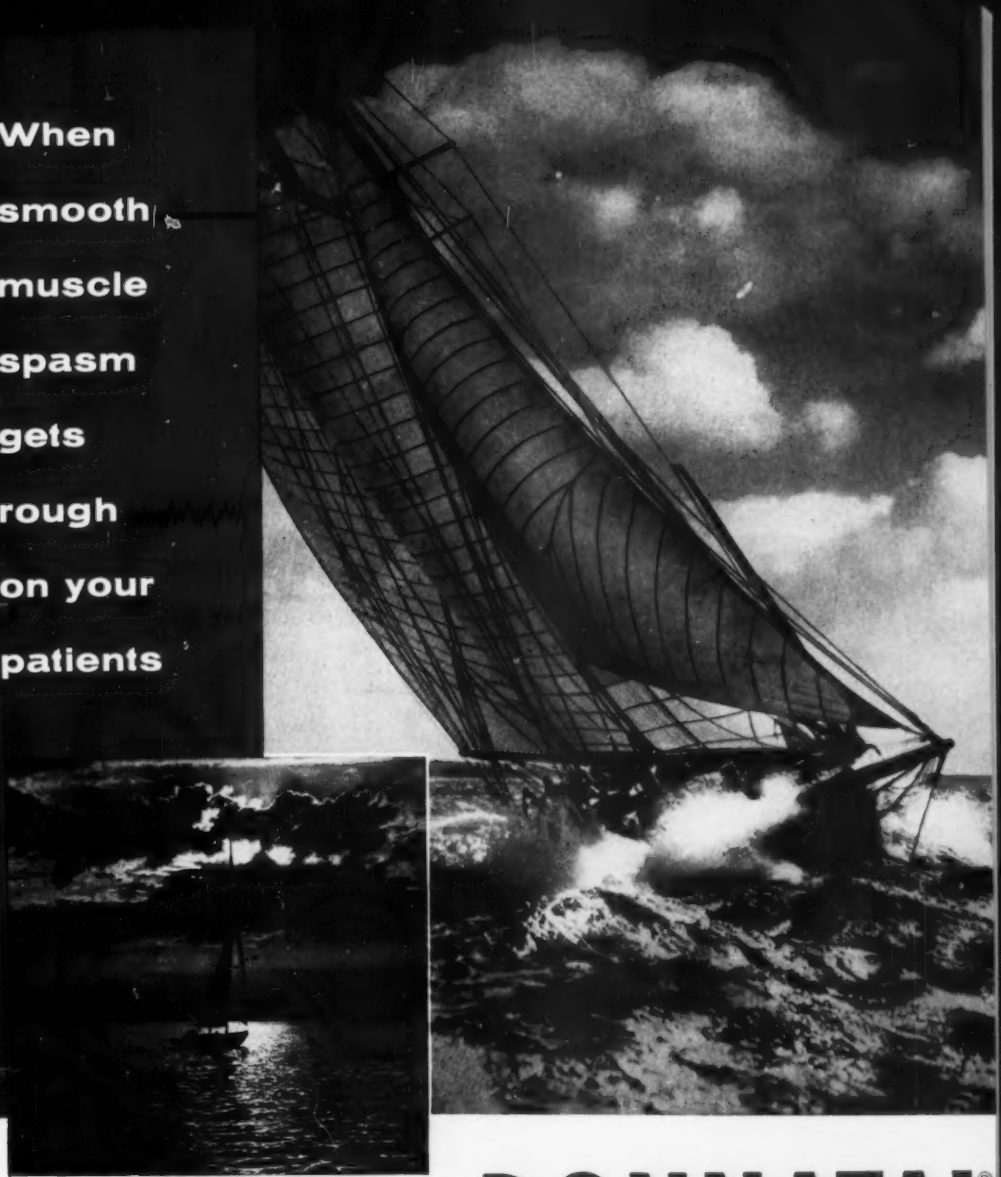

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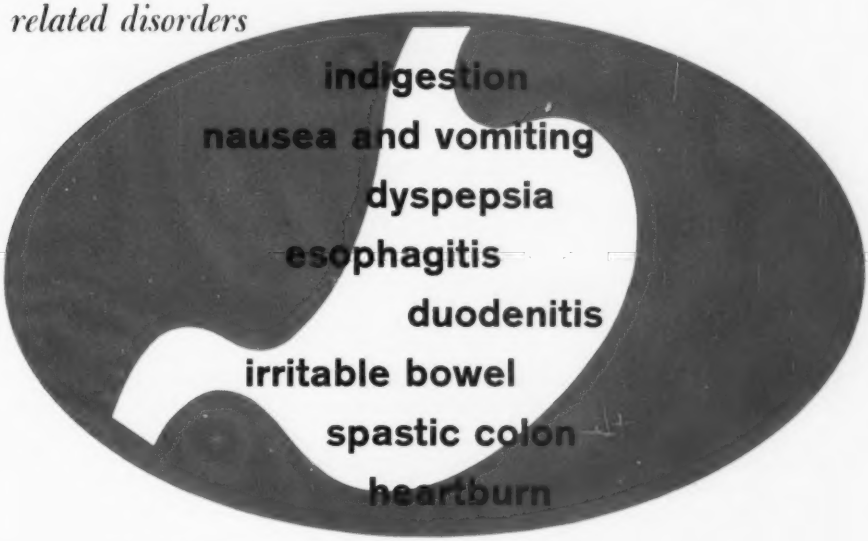

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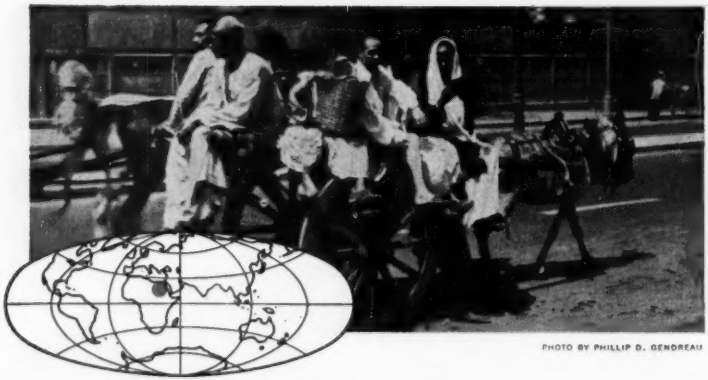

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Musgrave, M. E., and Arm, H. G.: Antibiotic Med. & Clin. Therapy 7:17 (Jan.) 1960.

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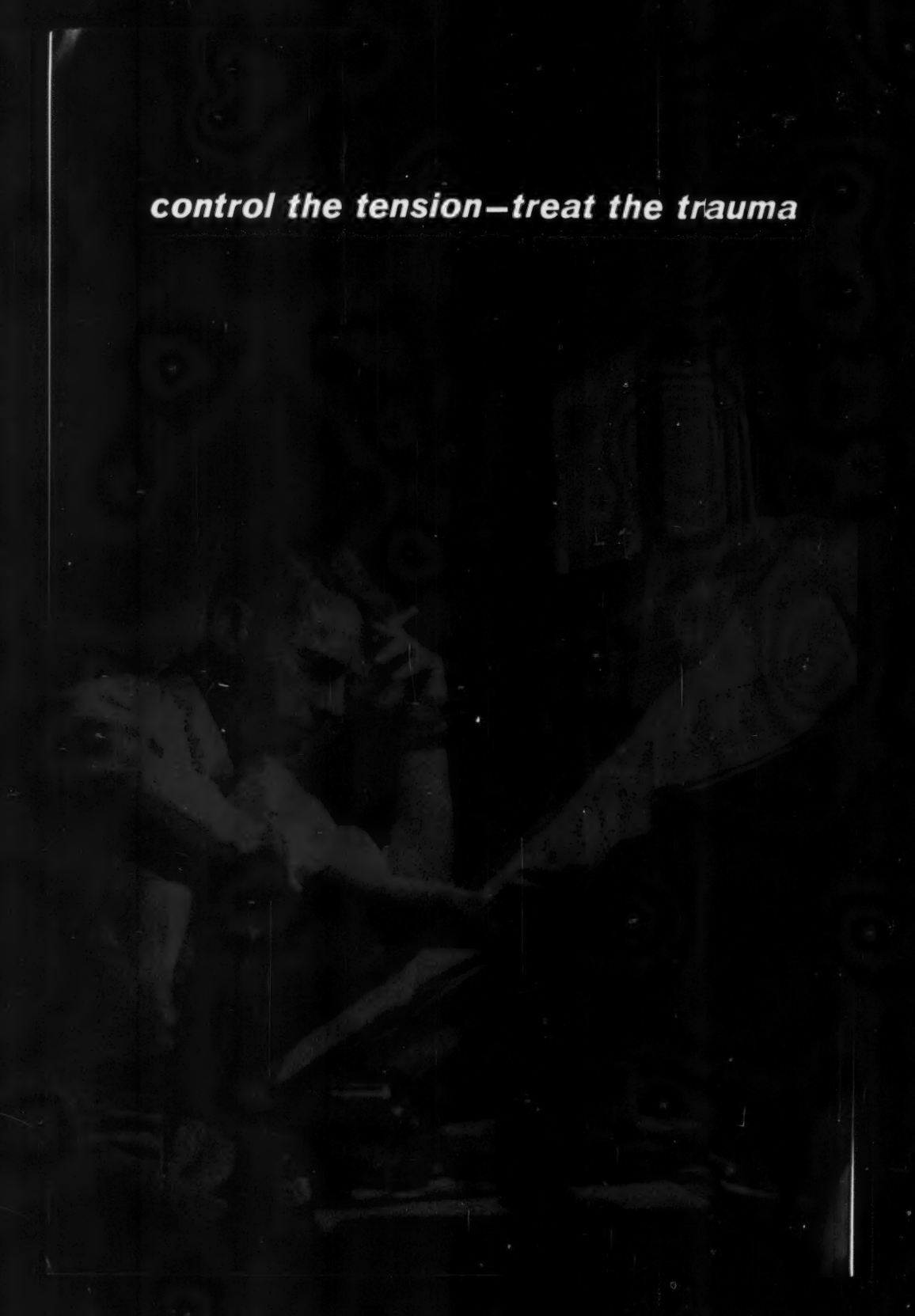
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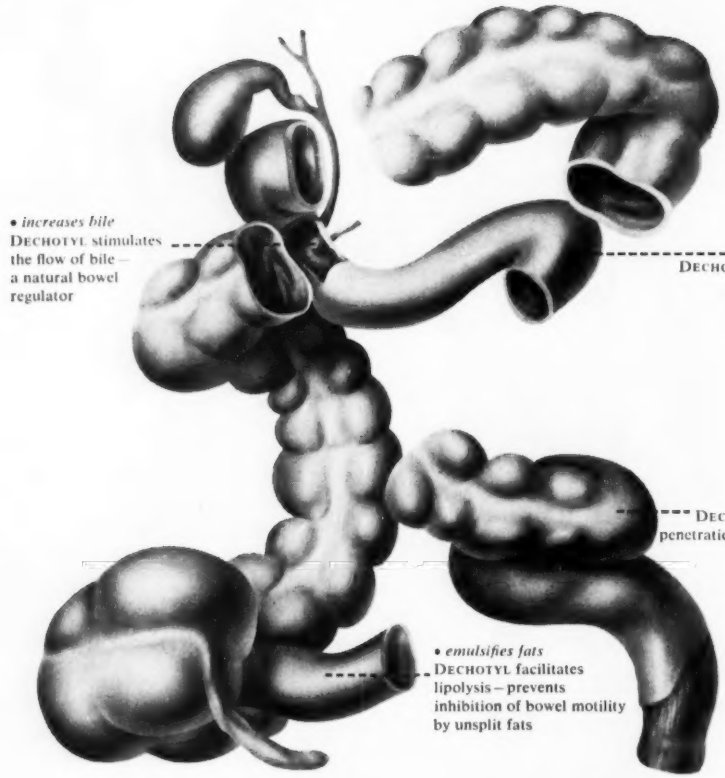

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VOLUME 33 JUNE, 1960 NUMBER 6

PANEL DISCUSSION ON GASTRIC ULCER IN 1959*

DALE W. CREEK, M.D., F.A.C.G., *Moderator*

D. R. DICKSON, M.D.

WILTON A. DOANE, M.D.

C. A. DOMZ, M.D., F.A.C.G.

JEROME A. ECKER, M.D., F.A.C.G.

and

JOHN A. KNIGHTS, M.D.

Santa Barbara, Calif.

Dr. Dale W. Creek:—Dr. Domz, on the right of the table, is on the staff of the Sansum Medical Clinic in Santa Barbara in Medicine and Gastroenterology; Dr. Ecker, next to him, is on the staff of the Santa Barbara Clinic as Chief in Medicine and Gastroenterology. Next to him, on his left, is Dr. Doane, who is Chief of Surgery, St. Francis Hospital and Surgeon at the Santa Barbara Clinic; next to Dr. Doane is Dr. Knights, Chief of Radiology at the Sansum Medical Clinic; and next to Dr. Knights is Dr. Dickson, who is Pathologist at the Santa Barbara Cottage Hospital.

Our purpose is not to present anything particularly new and different from 1958 or 1957, or probably what will be different in 1960. Rather what we wish to present is the importance in differentiating between duodenal ulcer and gastric ulcer; that they might almost be considered as two different diseases in their importance. We are presenting two representative cases to illustrate what we mean, and to show that the radiographic criteria of healing and so forth cannot always be taken at face value, and the clinical evaluation of this must always be of prime importance. I will go over these very rapidly.

Case 1:—A 69-year old white woman who had a diagnosis of gastric ulcer elsewhere in January of 1958. She was placed on strict ulcer management

*Presented before the Course in Postgraduate Gastroenterology of the American College of Gastroenterology, Los Angeles, Calif., 24, 25, 26 September 1959.

with a remission of symptoms. In March of 1958 and again in September, 1958, x-rays had shown progressive but not complete healing of the ulcer.

In October of 1958, the patient had again experienced burning epigastric distress, and at this time we saw her, and she was complaining that she had heart trouble, because, she said, her ulcer trouble had been taken care of. It was interesting that the pain would come late in the morning, two hours after lunch, and two hours after the evening meal.

Between November of 1958 and January of 1959 she lost eight pounds. Physical examination normal except for a blood pressure of 190/100. Upper gastrointestinal series showed an ulcer three-quarters of an inch in diameter with a base spreading out to involve one and three-quarter inches of stomach. Gastric analysis showed six degrees of free hydrochloric acid and 14 degrees total acid without histamine stimulation. Sedimentation rate was 61 mm. (Westergren) in one hour. X-ray studies after three weeks of strict ulcer management showed the same gastric ulcer practically unchanged.

Subtotal gastrectomy was performed. The ulcer had perforated, was adherent to the lesser omentum. Recovery was uneventful. Histologic findings were those of chronic peptic ulcer.

Three months after operation x-rays showed no disease and complete blood count was normal. She had gained five pounds and was without symptoms.

I think at this time we should have Dr. Knights show the x-rays on the first case.

Dr. John A. Knights:—(Slide) This first slide was taken in January of 1958 and shows the gastric ulcer on the lesser curvature side of the *pars media.* At that time, on the film, it measured about 1½ cm. in diameter and about ⅛ cm. in depth.

(Slide) This next one was taken about nine weeks later, in March of the same year, and shows very definite decrease in the size of the ulcer.

(Slide) The area of ulceration is in this vicinity. At that time it was considered to be practically healed. I think if you look closely you can see the very slight remaining infiltration.

I might say here that often, even though on x-ray we see what is complete healing, at gastroscopy complete healing has not taken place.

(Slide) This next slide was taken about one year from the first one, and shows recurrence of a large gastric ulcer on the lesser curvature side of the *pars media.* At this time it was about 4 cm. wide and 1 cm. deep.

(Slide) The patient was x-rayed for the second time about three weeks later, and you can see some change. It is about the same size, but it has changed

somewhat in shape and is not quite so deep. It was at this point that it was decided to perform surgery on the patient.

(Slide) The last slide, taken in May of 1959, some four months later, shows the postoperative stomach.

Dr. Creek:—Thank you, Dr. Knights.

Dr. Dickson, would you give us the pathological slides on Case 1?

Dr. D. R. Dickson:—On the lesser curvature, 5 cm. above the pylorus was a drop-shaped ulcer crater 10 mm. in diameter and 5 mm. deep. Radiating over the ventral surface from the rim of the ulcer was a scar 20 mm. long.

(Slide) This is a low power view of the active portion of the ulcer which has penetrated completely through the muscularis mucosae. The base of the ulcer shows the conventional four zones of peptic ulceration, the radiating fibrosis, and one vascular sclerosis characteristic of chronic peptic ulceration.

(Slide) This shows the healed portion covered with completely regenerate intestinal-type mucosa. Absence of muscularis mucosa, and submucosal and muscularis fibrosis are evidence of old penetration into the muscularis.

(Slide) This shows the regenerated epithelium at a higher magnification to emphasize the intestinal metaplasia, and the next (slide) is a gross photograph of another specimen, showing the pebbled mucosal state of real chronic gastritis associated with two small ulcers in the duodenum.

Dr. Creek:—Thank you, Dr. Dickson.

Dr. Ecker, would you talk just a little bit on how you feel medically or surgically that gastric ulcers should be handled?

Dr. Jerome A. Ecker:—I am an internist, and I feel every gastric ulceration must be treated as a potential malignancy and to a conclusion. Carefully repeated x-rays must be done, to be sure the size of the ulcer is shrinking not only in depth but also in transverse diameter. We feel that any ulcer crater that does not heal in three weeks with careful therapy, or fails to disappear completely in six weeks, should have gastric resection. Surgery is urged immediately when cancer is suspected, or reappearance of gastric ulcer demands surgery.

I think it is also important that a patient be thoroughly briefed on this problem, and he should give 100 per cent cooperation. He should be told it will be a 12 to 18 months stand, and if his ulcer doesn't heal in three to four weeks he should be prepared for surgery.

First of all, however, no criteria are infallible in individual cases. You all know gastric carcinoma is almost unknown in the first decade and is rare in the second decade, and it is common in persons over 35.

Certainly heredity would be a factor; certainly the predominance of carcinoma patients who are of Group B; racial susceptibility we are all aware of. It is twice as common in the Japanese race as in the Caucasian. A long history would tend to suggest a benign process; a short history would suggest cancer. Certainly if there is a change in a man's distress it would favor malignancy.

I feel that the measurement of gastric secretion is important and it is a useful test, but it is often a misunderstood procedure. As you know, there are four major patterns that we see: Normal gastric acidity, hyposecretion, hypersecretion, or anacidity. You must remember, on the other hand, that 20 per cent of normal men in the base line period will show anacidity and 30 per cent of healthy females. Eight per cent of healthy people will show an anacidity after histalog.

Palmer and Kirsner's series showed 15 per cent of their cases of gastric carcinoma originally with normal x-ray films, and actually there were 20 per cent in which gastric x-ray abnormalities were not diagnosed as cancer.

These ulcers, if they are benign, should be followed by cytologic studies, as done by Palmer, until the ulcer has completely disappeared. Kirsner reported 95 per cent accuracy in the University of Chicago laboratories, which is very good in cytology. I again would use gastroscopy to confirm the x-ray diagnosis and to supplement x-ray when there is any question.

I wouldn't want all of these criteria, probably, to be met before we treat the patient medically, keeping in mind that we have certain things we want to do. First of all, the healing of the gastric ulcer during the acute attack; second, the treatment of the patient in an effort to prevent recurrent episodes as a high percentage of these ulcers may recur in a two-year period. Third, attempt to treat any ulcer complication. This naturally will mean a long range medical program and at times a lifelong program because, as you all know, the cause of ulcer is still not understood, and our present medical regimen is based on the general principles that to relieve pain and to heal a peptic ulcer, gastric acid should be neutralized, its secretions should be inhibited or eliminated and the motor activity of the stomach and duodenum must be reduced. Efforts also must be made to resist the resistance of the gastric mucosa against any hostile pepsin factor.

Therefore, briefly, to heal an ulcer we want: 1. A restricted diet, 2. antacids, 3. antisecretory and motor inhibitor drugs, 4. absence of smoking, and absence from stimulants such as coffee and alcohol, 5. sedation, 6. and last but not least, getting all of the physical and mental rest that you can.

Dr. Creek:—Thank you Dr. Ecker.

Before we bring the sleeper case up here that will sort of emphasize what you said, Dr. Domz, can you say a word to us about some of the complications we might run into?

Dr. C. A. Domz:—In recent years a number of internists have been stampeded by surgeons who say that every gastric ulcer is a surgical problem. They quote statistics which show that 5 per cent of gastric ulcers are cancer to begin with, and within five years 5 per cent more will prove to have cancer.

Medical management of gastric ulcer has given poor results. Cain has cited experience where, of a group of about 400 small gastric ulcers, almost 40 per cent of the patients after five years got tired of medical treatment and eventually had surgery.

One of the objections to subtotal gastrectomy as routine treatment of gastric ulcer is the nutritional impact on the patient. Stocky and chubby patients will do well. The weight loss induced is probably a good thing anyhow. In some of these patients this weight loss is an extra dividend, and represents a lifelong dream of the patient, to be slim and fashionable and desirable.

In patients who are lean and underweight to begin with, however, the nutritional impact can be disastrous and almost as undesirable as the original disease, and makes some of these people wish they had taken their chances with their ulcer.

In Eddy Palmer's series of subtotally gastrectomized patients, full one-third were 25 pounds or more below preoperative weight a year after operation.

An illustration of the problems you run into is a 51-year old housewife whose ulcer is shown on the next slide.

(Slide) I am sure you can all see this tremendous ulcer crater 4 cm. in diameter on the left curvature side of the stomach.

(Slide) This is a slide made about three weeks later, which shows very definite decrease in its size. This ulcer was described by one radiologist as a typical "mailbox ulcer".

This patient had had pain for six months, and with the incidence of carcinoma approaching 40 per cent in giant gastric ulcers there seemed to be little doubt as to the need for prompt surgery. But she weighed only 87 pounds. She had never weighed much more, and the necessary three-quarter gastrectomy would have made a permanent nutritional cripple of her.

The ulcer was, by history, a recurrence of a gastric ulcer which had occurred 15 years earlier, and this is a little too slow for a gastric neoplasm. Gastric cytology was negative.

Improvement was shown in three weeks, and since there was approximately 50 per cent healing we continued the program of diet, medication, and rest. The latter was completely exploded. When her relatives heard of her serious illness they came in from several states to be with her and, as is common in California, they decided to "set a spell". The patient wound up with 16 house guests for

whom she had to rent three double beds and a tent in the backyard. Her grocery expenses prevented her from entering the hospital.

(Slide) After three harrowing weeks of this "togetherness" this last film shows, amazingly enough, complete healing of the previous gastric ulcer. It was taken about one month after the second slide.

Of course she will have to have follow-up x-rays two, four, six, eight months, a year, to show that this ulcer has not recurred. She is gaining weight. She is up to 94 pounds, and every pound we can put on her will reduce the risk that much more, should operation become necessary.

I don't think we have time today to go into the dumping syndrome or the fact that stump carcinomas do occur after resection of a gastric ulcer. I think the approach to gastric ulcer has to be one of thoughtful consideration, with careful follow-up.

Dr. Creek:—Thank you, Dr. Domz.

The next case makes me think of the boy who woke up on a stretcher with a sheet over his head and he asked the stretcher bearers, "Where are you taking me?"

They said, "We are taking you to the morgue."

He said, "There must be some mistake. I'm not dead."

They pushed him down and said, "Lie down. What do you want to do, make a liar out of the doctor?"

I hope you remember what Dr. Ecker had to say in his very excellent summary of the literature and the criteria for judgment of how to treat an ulcer, because this next case makes a liar out of all of us.

Case 2:—This was the case of a 40-year old man first seen 9 December 1957, with a history of gastric distress since 1955, increasing during the previous eight months. The Ewald test showed 14 degrees of free hydrochloric acid, 33 units of total acid, electrocardiogram showed incomplete right front and branch block, narrowing of the antral portion of the stomach, ulcer crater in the pylorus and a suggestion of a larger ulcer crater on the greater curvature. In one hour there was satisfactory emptying.

Gastroscopic examination was inconclusive as the pylorus could not be adequately visualized. Antispasmodic sedation before meals and at bedtime. In the next two weeks he became entirely free of symptoms and he gained five pounds in weight. After five weeks of therapy, repeated upper gastrointestinal x-rays but no ulcer craters were seen.

The patient reluctantly consented to surgery, was explored on 7 January 1958. There appeared to be chronic gastric ulcer at posterior wall. There were a few nodes palpable about the pylorus. Gastric resection was done.

Dr. Knights:—(Slide) This slide shows it perhaps not too well. The next slide will show better what we are talking about. There was a very definite prepyloric narrowing and rigidity in this area. It was not only the question of an ulceration being on the lesser curvature side but also on the greater curvature side.

(Slide) These are spot films, and again you can see the prepyloric narrowing and rigidity. I think at this point the ulcer crater on the greater curvature side is well depicted. The one on the lesser curvature side in this particular group of films I am not very sure of. These films were taken in December, 1957.

(Slide) This examination was repeated about three or four weeks later, and both at fluoroscopy and on the films it was thought the ulcer craters had healed. There was very definite prepyloric narrowing and rigidity.

I might say that the impression on the first slide was that it might be in the pyloric canal. Certainly carcinoma could not be excluded.

(Slide) These are spot films on subsequent examination, which again show the prepyloric narrowing and rigidity. Again it was thought that it was most probably a carcinomatous lesion.

Dr. Creek:—Dr. Dickson, would you now give us the gross and microscopic findings on this?

Dr. Dickson:—I did not examine the gross, but I understand there was definite induration and a shallow scar in the prepyloric region, and I gather the pathologist was suspicious but not too suspicious. He was somewhat surprised when he saw the microscopic section.

(Slide) This shows a concavity lined with irregular atrophic mucosa. There is a definite defect in the muscularis mucosa and submucosa; the muscularis is greatly thickened and there is considerable scar and inflammation through it. There is carcinoma in the mucosa here, and the next (slide) a higher magnification shows the pattern of the superficial glands with an infiltrating carcinoma, with varying degrees of differentiation.

Dr. Creek:—Thank you very much, Dr. Dickson.

I think it is interesting to note that this case met most of the criteria for medical satisfactory treatment of gastric ulcer. It was only the high index of suspicion on the part of the radiologist, who felt that he wasn't satisfied with the stiffness of the pyloric segment, and fortunately, even though reluctantly, they were able to get this man to surgery.

Dr. Doane, would you now make a few comments on how you feel surgically in general about gastric ulcers?

Dr. Doane:—As a surgeon, I feel that the patient should be explored immediately when a diagnosis of gastric ulcer is made. There is, however, one thing

about gastric ulcer '59 that differentiates it from gastric ulcer '49, in that the medical and surgical views in the treatment of gastric ulcer are converging.

I believe, speaking of gastric ulcers and not of ulcerating lesions that are probably carcinoma to begin with and should be explored at once, that gastric ulcers should all have a preliminary period of trial management of three weeks. If at the end of three weeks the x-ray is not completely negative, if the patient is not completely asymptomatic, and if blood is found in the stool, then exploratory laparotomy should be performed at once. Of course it is well known that the difficulty in making a gross diagnosis is sometimes greater than that of making a radiologic diagnosis between an ulcer and a carcinoma, so we must utilize various aids in trying to determine the diagnosis. First, a search should be made for metastatic tumor in lymph nodes or liver invasion of the pancreas. Either of these very often will tip the surgeon off as to the character of the lesion. Examination of the stomach by palpation, of course, aids some, by showing the size and depth of the ulcer and the amount of infiltration. A gastrotomy is a useful aid, and frozen section diagnosis is very often helpful.

If a lesion is not malignant, then a partial gastric resection should be performed, including the omentum and spleen if indicated. If the spleen is very high it should be removed.

If there is an infiltrating lesion, it is important to do a frozen section and examination of the end of the specimen to be sure that the lesion had not advanced beyond the end of your resection.

I feel that total gastrectomy should be avoided if at all feasible technically, because of the fact that these people are nutritionally in a bad state on most occasions. If the ulcer is benign, then I feel a 50 per cent distal gastrectomy should be performed.

A negative biopsy certainly does not rule out the possibility of carcinoma. This is especially of value in situations where gastric ulcers invade the pancreas, and to do a section which involves only a portion of the pancreas one therefore greatly increases the risk of the procedure, and very often by doing a total resection diagnostically the procedure can be facilitated.

Ulcers of the stomach present an entirely different problem. If the lesion is small, grossly benign, and the patient is a poor risk, old, I feel that the palliative distal gastroresection is probably as good a method of management as any.

I would like to add one thing, that prior to surgery steroid and histamine therapy is indicated also.

Dr. Creek:—Thank you very much, Dr. Doane.

Dr. Knights, could you give us just a few of the criteria you feel radiographically might be used to distinguish between benign and malignant gastric ulcers?

Dr. Knights:—So far as the radiologist is concerned, I think we have about five things to consider in distinguishing a benign from a malignant gastric ulcer.

First I might say that what we should try to do, is to detect the small ulcers; then try to, if at all possible, distinguish between the benign and malignant ones.

The third thing which I have to mention is to keep the radiation as low as possible to the patient. We also should consult with the internist as to the frequency of the re-examinations for demonstrations of the ulcer.

The five things I mentioned at first I think are: location, then size, disappearance, rugae pattern, and the shape. These five things I think are very important when we try to distinguish a benign ulcer from a malignant one.

Much has been said through the years as to what size has to do with whether an ulcer is benign or malignant. I think a few years back, primarily through the work of Carman, it was realized that size was very important. The larger the ulcer, the more apt it would be to be malignant. While I don't think this is entirely true, we have to take this sign with reservations, because many large ulcers, as you know, are of a benign variety.

I think location has to be taken with reservations, too, because it has been estimated by some men that at least 50 per cent of the ulcers on the greater curvature side are benign.

Shape, the third point, again should be taken with reservations. We cannot tell, I think, exactly by the shape of an ulcer whether it is a benign one or a malignant one. So that I think the location, size and shape should all be taken with reservations, and the two remaining, that is, how long does it take the ulcer to disappear, and the appearance of the rugae which lead to the ulcer crater, are important. Lloyd in his series of some hundred ulcers, noted that in all of the benign ulcers there was no interruption of the rugae pattern as it led to the crater, whereas in 90 per cent of the malignant ulcers there was a very definite interruption of the rugae pattern as it led to the crater.

So, in summary, I believe that the appearence of the rugae pattern, and whether or not the ulcer disappears in from two or three weeks, are most important criteria.

So far as x-ray diagnosis is concerned, I think when we diagnose them as malignant and they are found to be benign our error is about 9 per cent. On the other hand, when we call them benign and they turn out to be malignant the error appears to be about three to six per cent.

Dr. Creek:—Dr. Dickson, one or two questions before we close that I would like to ask you from your experience. You catch all of our mistakes.

I would like to know if gastric ulcer is increasing or decreasing, in your experience; what the role of cytology at the present time is, and what you find to be the incidence of gastric ulcer at surgery as compared to postmortem.

Dr. Dickson:—Let's take the last question first. Of course in surgical specimens you have a higher incidence of duodenal ulcer than of gastric ulcer. Our hospital sees about two duodenal ulcers to one gastric ulcer in surgical specimens. In a ten-year review of our autopsy material of over 100 cases showing peptic ulceration we found a proportion of almost two and one-half gastric ulcers to one duodenal ulcer, the implication being that either gastric ulcer is not diagnosed as frequently or it is a more fatal disease.

Regarding cytology, there is no question that it is very valuable. The teaching centers have established this. There they have fairly elaborate teamwork programs, and they obtain beautiful results. In a small hospital we can't develop these teams, for a number of reasons, but we have discovered that we get very satisfactory results by following the same technics so far as preparation of the patient and aspiration of the material, but we place the aspirate at the bedside without delay, into 70 per cent alcohol, and we are satisfied that we get very good cytologic results.

Our experience, regarding gastric carcinoma, is too small to draw any conclusions about incidence rates. Our gastric carcinomas have run 8 to 10 a year since 1956, and last year we had 7. This is not statistically significant. The statisticians of the American Cancer Society and the insurance companies who wait for a definite trend before they commit themselves do say that gastric carcinoma appears to be on the decrease.

Dr. Creek:—Thank you very much, Dr. Dickson.

I am sure this is something we can talk about indefinitely. If there are any questions, however, from the floor, we will be happy to direct them to any of the panelists whom you care to ask. You will either stand up and give your name or, if you have a written question, bring it forward.

Dr. Herman Smith (Baltimore, Md.):—I would like to ask the pathologist in his incidence of two and a half times the number of gastric ulcers at autopsy, what was the criterion for calling it a gastric ulcer?

Dr. Dickson:—A penetration through the muscularis mucosa. In breaking that down, 72 per cent were superficial and 28 per cent were penetrating into or through the muscularis. Superficial agonal erosions were not included.

Dr. Creek:—Are there other questions?

Question:—I would like to know what is the incidence of recurrence of gastric ulcer when the ulcer heals from medical management, and also the history of recurrence following surgery; and, in surgery, what is the recommended management for recurrence of gastric ulcer that has been treated medically?

Dr. Creek:—Dr. Ecker, would you like to discuss the first?

Dr. Ecker:—According to Davis, in patients that have benign gastric ulcer, in five years if those patients are carefully followed about 30 per cent will recur with gastric ulcers.

Dr. Doane:—I can't state statistically what the recurrence is, and it would depend on what sort of procedure was performed. In my opinion, however, it is rather low, unless the gastrectomy is insufficient.

Dr. Creek:—I would like to make one comment on that. You would have to break that down as to when the surgery was done. If this was an operation done in 1929, for instance, I think we see a fairly high recurrence rate of stomal ulcers; perhaps not so much in gastric ulcers. If this was done more recently, with the surgery as described by Dr. Doane, I think the incidence is very low.

Question:—The recommended management of recurrence of gastric ulcer which was treated medically is what?

Dr. Domz:—If so-called benign gastric ulcer is healed medically and then recurs, I would favor gastric resection. These are the ulcers that are deep; they tend to bleed; they tend to penetrate, and if the patient has none of Dr. Doane's contraindications, I would recommend surgery.

Dr. Ecker:—Would you think that management for the second occurrence should be different from that for the first occurrence, providing you can demonstrate the diminishing effect by x-ray, and so on? What causes you to recommend surgery then? Maybe he got out of bed early. Maybe his wife was giving him a bad time.

Dr. Domz:—In a large series the experience with medical management of gastric ulcer so far as recurrence is concerned was not good. Only 20 per cent of patients in this series did well over a long period of time.

Dr. Creek:—Dr. Domz, I will direct this question to you. It is a fairly long question. I won't read it all. It has to do with the use of steroid therapy for rheumatoid arthritis, and so on. What is your opinion about the occurrence of gastric ulcer, and how cautious would you be in withholding steroid therapy or not using it promiscuously, because of the possibility of developing gastric ulcer on such management?

Dr. Domz:—There are several problems involved in that question. I think the first thing to be settled is that steroid therapy should never be used promiscuously, because it is a loaded weapon. If you use it, be prepared to follow

through. If there is a history of ulcer you must be doubly watchful. Once in a while you have the problem of steroid therapy needed for a very urgent reason: the patient is taking steroids for a crippling, disabling disease, and without steroids he would be a bedridden cripple, whereas with steroids he can get on the job. He has a gastric ulcer. I think the only recourse you have there is to perform surgery for the gastric ulcer.

This will first of all settle the problem of whether the ulcer is malignant or not; and secondly, having removed the ulcer, you greatly decrease the patient's capacity for producing further ulceration.

Dr. Creek:—There are two parts to this question. Dr. Doane, would you care to comment on the first part: concerning the large majority of ulcers clinically, radiographically and gastroscopically which appear benign and then prove at surgery to be malignant, as in the case we presented here. In other words, how strongly do you feel that we should go further in trying to eliminate malignancy in one that is clinically proved to be benign?

Dr. Doane:—I think you have to use a fairly common sense view in attempting to treat a gastric carcinoma because of the fact that even though the incidence of cure is improved with early operation, and this has been proven without any question, still the incidence of cure is not greatly improved, and in order to cure a very, very few more patients you have to inflict an operation on a lot of people with subsequent complications that are almost inevitable.

I feel just as I stated in my previous comments, that we have to have a certain set of standards, and healing at the end of three weeks, absence of symptoms, and lack of melena are the most important. So that I don't feel that we should make any more stringent statements regarding doing a gastrectomy on all gastric ulcers, or even earlier.

Dr. Creek:—I think actually this was pretty well covered in Chicago at our meeting there four years ago, when Dr. Ochsner was beating the drums very much: A person past 40 who has lost 10 pounds of weight without dieting, that that person should be explored, and statistics show that less than one out of ten with that criterion are found to have pathology, and Dr. Snapper got up and said, "I am quite sure if such a distinguished surgeon as Dr. Ochsner should tell me that I should have an operation, I would probably have it, but I am on the staff of three hospitals and," he said, "if we had a young surgeon come in who brought us nine normal stomachs, I am afraid that the surgeon wouldn't last very long on our staff."

On the other extreme we have the group who feel very much that all gastric ulcers, with minor reservations, should be treated medically and should be followed for a much longer period of time.

The other part of this question: "How about the ulcers that aparently heal on medical regimen and then recur later as malignancy?" Dr. Domz, would you like to comment on that?

Dr. Domz:—This is a definite risk. There is a certain amount of that that nobody can obviate. First, after partial gastrectomy for ulcer, a number of cases develop cancers in the gastric stump anywhere from 5 to 30 years after operation. It's unreasonable to assume the tumor was there that long, although we know that some tumors can be very indolent.

Then, too, there is the chance that the ulcer did heal and subsequently recurred and all along was a cancer. I think the dictum still holds, that a cancer can ulcerate, but ulcers don't "cancerate", so you probably had a cancer to begin with. The only way you can reasonably get around this pitfall is to follow it up carefully and for a long enough period of time.

While I have the floor I would like to make one comment on this figure we have heard repeatedly about healing in three weeks. General experience indicates that an acute duodenal ulcer will heal in about six weeks. I don't feel that it is reasonable to expect the stomach to heal faster, so that in most instances if you can demonstrate 50 per cent, or roughly 50 per cent, healing in three weeks you are making good progress, and you can go another three weeks.

At the end of six weeks, however, you must insist on complete disappearance of all x-ray defects. If there is the slightest trace of x-ray abnormality, you have no recourse but surgery.

Dr. Creek:—I certainly agree with that, and we must remember that with most ulcers there is inflammatory reaction, and on a strict medical regimen this inflammatory reaction may disappear, and you may get a false impression that you are healing the ulcer itself. I think, therefore, as you said, if at the end of five, six, or whatever number of weeks you want to use, there must be complete disappearance.

Dr. Ecker, I have a question here. Perhaps you can help: "On those gastric ulcers which show insufficient improvement in three weeks to continued medical management, and they turn out to be malignant, what is the five-year cure rate?

Dr. Ecker:—Statistics on cure rate vary very much, and actually there is one patient reported from The Breslau Clinic who had a gastric ulcer at 31 years of age and had a 21-year cure. After all, the over all statistics reported by the Mayo Clinic give a five-year cure rate of 14 per cent in 100 patients. In another study of Palmer, 7 per cent of the patients survived five years. For the patients with preoperative so-called benign gastric ulcer their cure rate may go 40 or 50 per cent in cancer of the stomach.

Dr. M. Muehlbauer (New York, N. Y.):—One of the more difficult problems in the radiological diagnosis of the stomach is the early recognition of *linitis*

plastica. I would like to hear from the panel if they could give us anything on how to improve that recognition.

Dr. Ecker:—Of course it is a very difficult diagnosis to make. Cytology may be negative. Gastroscopy may be of help, because this is one instance where the stomach will not hold air. You can pump air into the stomach and it will pass out through the stiff, patulous pylorus.

Dr. Creek:—Dr. Domz, this question has been asked: "What would be your outline of an adequate medical regimen and how do you feel about cabbage juice, etc., etc."

Dr. Domz:—We still use the standardized medical regimen for treatment of gastric and duodenal ulcers. I think the first thing to do is to have physical and mental rest. A man may need to get away from his family; a mother may need to get away from her children. Sometimes it is best for the patient to see a rabbi, priest or minister.

Then, adequate neutralization of acid. You have to insist that during this six-week management period the patient eat at least six times a day, in addition to which he takes between-meal antacid every half hour. Every 30 minutes something is going into his stomach that acts as a buffer.

Beyond that there is some disagreement. My personal preference is that the patient be given a mild sedative, and my personal preference is phenobarbital combined with an anticholinergic. With regard to the latter, we find various claims. I don't think any of them has really proven to be superior to Pro-Banthine.

With regard to unusual forms of treatment: cabbage juice, Vitamin C and every vitamin that has ever been discovered, and even a few hormones, have been advocated. None of them has ever proved to be of real value except in the hands of the original man writing the paper, and then sometimes in only two or three cases.

Dr. Creek:—Thank you, Dr. Domz.

Our time is limited. We could go on indefinitely with this. Those of you who are going to the afternoon meeting, I think, however, should be aware of the hour. We appreciate your interest tremendously. If there is any other pertinent question we will be happy to answer it.

SOME RECENT ASPECTS OF FAT METABOLISM*

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The layman along with most nutritionists realizes the importance and necessity of proteins, vitamins and salts in the diet. They have, however, considered that fats and carbohydrates are optional foodstuffs which can be used in the proportions desired to make up the necessary calories in order that the caloric intake be adequate. This concept is quite fallacious. The sooner we realize that the tissue fats are essential; that the body synthesizes saturated fats, mainly from ingested carbohydrates and proteins as well as from the fat of the diet, the sooner we will come to grip with the dietary problem.

Secondly, fats have been maligned since they are believed to aid in the development of arteriosclerosis and coronary heart disease. The consensus of opinion of large numbers of physicians is that animal and vegetable fats serve equally effectively in producing cholesterol since this sterol originates mainly from the acetic acid molecules formed from the oxidation of the fatty acids. There is ample proof, however, that no greater amount of cholesterol is manufactured in the body on a high fat diet than occurs in diet high in carbohydrates or protein.

Thirdly, there is an increasing amount of evidence which seems to suggest that fats may be guiltless as causes of arteriosclerosis, and that they may actually in some way act to prevent the development of this condition. The final answer is not known. Let us review briefly what is known about fat metabolism.

The oxidation of fatty acids can be summed up in Figure 1 showing factors and co-factors necessary for the reactions to take place. The last reaction is a thiolytic split instead of hydrolytic thus giving rise to a "new" activated fatty acid with two carbons less, giving off "active acetate".

The tricarboxylic acid or TCA cycle is a major pathway for the final oxidation of carbohydrates, fats and proteins. Each turn of the cycle oxidizes one mole of acetate to CO_2 and water thus releasing about 200 calories of energy. Some of this energy (about 144 calories) is captured by formation of ATP; the

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remainder occurs at heat. To illustrate, the oxidation of metabolites is a source of energy within cells. Let us take as an example the oxidation of the metabolite ethanol, Figure 2. Co-factors required during this reaction are also illustrated in the same figure. In other words, there is a three-step degradation of metabolites. At each step a high energy phosphate bond is formed. Figure 3 further illustrates in a simple way the degradation. At this point mention should be made of the necessity or presence of zinc ions during the oxidation of ethanol. Thus alcoholics and patients with Laennec's cirrhosis generally manifest faulty or abnormal zinc metabolism. This is brought about by the increased demand for this metal coupled with the inadequate dietary intake by these people. Each step in the degradation of metabolites represents the capturing of calories and involves oxidation coupled with phosphorylation. Each bond on hydrolysis will yield between 10 to 12 kilo calories. For each atom of oxygen that is taken up,

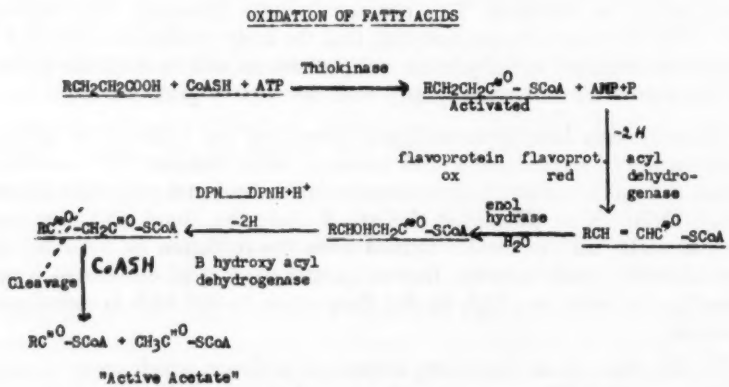

Fig. 1—Oxidation of fatty acids showing factors and cofactors.

three atoms of phosphate are incorporated into high energy bonds. Thus the P/O ratio is 3 to 1. Mention before was made about oxidation coupled with phosphorylation; this is not an obligatory step. In coupling we have great efficiency and storage of energy. We have also uncoupling, the free energy of the respiratory process is lost to the cell and appears as heat. Thus uncoupling is a valuable device to balance coupling to maintain body temperature in warm blooded animals. So, for every mole of active acetate oxidized there is formed 12 moles of adenosine triphosphate (ATP): 3 at oxalosuccinate, 4 at alpha ketoglutarate, 2 at succinate, 3 at malate.

Thus, in ketosis as in uncontrolled diabetes mellitus where there is an accumulation of ketone bodies, normalizing of the TCA cycle is desirable instead of loss of ketone bodies in the urine. In the diabetic we get an accumulation of these toxic substances because of their inability to enter the TCA cycle.

Absorption

Absorption is the passage of the breakdown products from the intestinal lumen into the blood or lymph systems. Reliable experiments have shown that the preferential pathway of fat transport depends on the chain length of the fatty acids. Chaikoff and his group found that regardless of the form in which fats are fed, the longer chain fatty acids appeared chiefly in the lymph while the fatty acids with less than 12 carbon atoms appeared in the portal vein[1-4]. Bollman and his group in their study stated that most of the products of fat digestion appear in the lymph. Two different groups (Fernandes and Bloomstrand) working independently showed that C8 fatty acids were not transported by the lymphatic pathway in man. This confirms in man the observation made by other investigators in rats. Consequently, it can be said that the products of dietary fat, since they are usually of the C16 to C18 variety, appear largely in the lymph. In chylous ascites, since it is usually due to rupture of the lymphatic system, there is pouring out of the long chain fatty caids into the peritoneum or pleural cavity. In portal obstruction there is loss of the short chain fatty acids

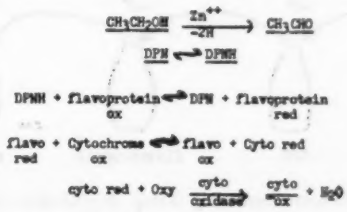

Fig. 2—Oxidation of metabolite ethanol showing required cofactors.

which may account for the weakness and the loss of weight in patients with cirrhosis of the liver. The loss of muscle volume may represent the pulling out of protein for energy calories. The associated "gastroenteritis" further produces malabsorption of all food products.

The exact form and mechanism by which fat is absorbed is not known; however, there is good indication that following hydrolysis, mono-, di-, and tri-glycerides as well as fatty acids are absorbed as finely emulsified particles with the aid of the bile. As early as 1932 Schonheimer et al were able to detect large amounts of cholic and desoxycholic acids from the bile of a patient with hepatic disease[5]. Normally these acids are found in the conjugated form, i.e. with glycine or taurine, at least to the extent of 80 per cent according to Colp and Doubilet[6]. These investigators also found large amounts of unconjugated bile acids in pathologic liver conditions. Magee and co-workers observed that a reduced secretion of cholate was indicative of liver dysfunction, and that a correlation exists between the mean deficit and the BSP (bromsulfalein) retention[7].

We observed recently a significant difference in fat absorption as shown in Figure 4 between patients with cirrhosis of the liver and normal individuals who were fed a measured amount of protein after an overnight fast. At two different sittings the normals were fed hydrolyzed protein on one occasion and nonhydrolyzed protein at another. The patients with hepatic cirrhosis at one sitting were fed hydrolyzed protein. As illustrated (Fig. 4), the normals showed a significant fall in total serum lipids after establishing the fasting level as a base. This fall was manifested with both types of protein. The patients with liver dysfunction showed no significant change over the same period and under the same conditions. We also observed an elevated fasting serum lipid level among the cirrhotics. It is rather difficult to explain the difference between the two groups. It would, however, be worth the time to take a closer look at bile secretion and flow in fat absorption. Bile plays an essential role in the digestive and absorptive phase of fat metabolism. Its salts activate the lipases to accelerate digestion and these, in turn, produce the solubilizing effect on the hydrolytic products.

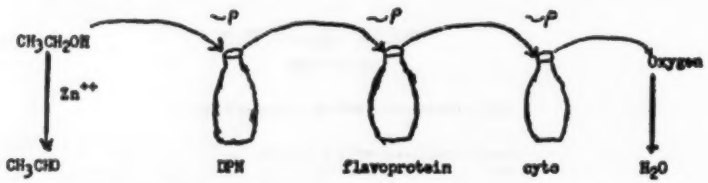

Fig. 3—Scheme illustrating 3-step degradation of ethanol.

Let us turn our attention now briefly to another steroid, cholesterol. Chaikoff has shown that cholesterol is transported entirely by the lymphatics, and none through the portal system[8]. It is also known that the absorption of cholesterol requires bile. It has been reported that with a cholesterol-free diet, the serum cholesterol levels of rats are higher with the more highly unsaturated fats[9]. Thus, dietary fats appear to have several effects on cholesterol absorption viz: stimulation of bile flow, provision of fatty acids for esterification and possibly other influences.

Alfin-Slater and her collaborators first demonstrated that the presence of essential fatty acids is required to aid in the regulation of the cholesterol in the blood and tissues[10]. This contribution has been widely accepted and proven by virtue of recent findings[11]. According to Alfin-Slater and others, essential fatty acid-deficient animals develop a syndrome characterized by scaliness of the paws and tail, capillary fragility, increased skin permeability, alopecia and ocular lesions. The loss of fertility in male rats, poor growth reflected in histologic bone changes, increased concentration of cholesterol in the liver and adrenal gland, and a reduced cholesterol content in plasma, also fat infiltration

of the liver have been reported. All of these changes were observed in animals deprived of the essential fatty acids in the diet. The clinical evidence brought forward by A. E. Hansen is rather striking in the light of Alfin-Slater's work. Infants fed on diets low in fat frequently develop changes in the skin consisting of dryness and desquamation, denudation, and exudation in the body folds. With the addition of 2 per cent of the calories as linolenic acid to the diet there was a complete reversal of the abnormality within one week to ten days. These findings would indicate the necessity of the essential fatty acids in the diet of man. There is, however, no valid reason today or experimental evidence to substantiate the condemnation of certain dietary fats on the basis of their origin or their saturation.

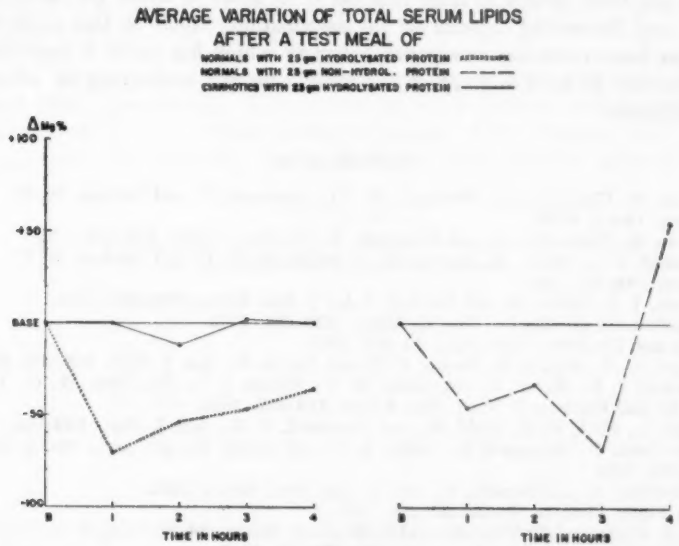

Fig. 4

At the turn of the century several investigators reported that the emptying time of the stomach was dependent upon the melting point and the viscosity of the fat ingested[12,13]. On the other hand, Hoagland and Snider in their experiments could not show any such relationship[14]. Deuel and his associates later showed an inverse relationship between melting point and absorption in the rat[15]. Working with rats and using a modified Cori technic, Pinsky et al showed that there were very little or no differences in stomach-emptying time when various types of dietary fats were studied (personal communication). In our studies with human subjects, it was found that fat absorption was not correlated with melting point or viscosity. In fact, butterfat was found to be absorbed more rapidly than the various other dietary fats studied. This conclusion was based

primarily on quantitative analyses and turbidimetric measurements of serum. Our studies seem to indicate that certain fats stimulate the fat-digesting and fat-absorbing mechanisms more than others. The exact mechanism is not understood.

Aside from the above mentioned factors concerned with fat absorption there are several others which we will mention briefly, namely: the effect of age, species and individual differences, structural configuration of the fat molecule, polymerization, and other food components present with ingested fat.

Summary

In this brief review attempt has has been made to avoid the more controversial and fluctuating aspects of fat assimilation. Much of this controversial work has been receiving newspaper notoriety which has made it important for the physician to have a grasp of the basic concepts underlying fat absorption and utilization.

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SOURCES OF MASSIVE GASTROINTESTINAL BLEEDING IN PATIENTS WITH LAENNEC'S CIRRHOSIS*

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The first reported case of ruptured esophageal varix in a patient with Laennec's cirrhosis was reported by the Frenchman Fauvel in 1858[1]. Since the review of the literature on the subject by Preble in 1900 it has been recognized that esophageal varices were the commonest, but not the only source of gastrointestinal bleeding in the cirrhotic[1]. At that time diagnostic means and medical and surgical treatment was limited, and the determination of the exact source of bleeding was largely of academic interest.

As the incidence of all types of cirrhosis is apparently increasing and it is estimated that approximately 30 per cent of these patients will have gastrointestinal bleeding at some time during the course of their disease; and, as the immediate and final mortality rate in cirrhotics with massive gastrointestinal

TABLE I

AGE OF DEATH FROM GASTROINTESTINAL HEMORRHAGE IN 100 CASES OF LAENNEC'S CIRRHOSIS (BY DECADES)

0 – 19 years	0
20 – 29 "	2
30 – 39 "	15
40 – 49 "	19
50 – 59 "	34
60 – 69 "	20
70 – 89 "	10
	100

hemorrhage is high, it is becoming increasingly important to detect the bleeding site in the cirrhotic and effect hemostasis promptly[2]. This depends on swift and accurate diagnosis.

Insufficient emphasis has been given to the fact that many cirrhotics bleed from causes other than esophageal varices. A brief search of the literature revealed only two papers on this subject in the past ten years[3,4]. As the treatment for hemorrhagic gastritis, peptic ulcers, gastric varices, tumors and hemorrhagic diatheses is considerably different than for bleeding esophageal varices, it becomes important to differentiate these lesions in the cirrhotics and to formulate an investigative approach which will most likely yield a prompt and accurate diagnosis of the site and cause of the bleeding. It is the purpose of this paper

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to present evidence on these matters and suggest a plan for the diagnosis and care of such a patient.

Methodology of Study

From the files of the Department of Pathology of the Los Angeles County Hospital approximately 390 unselected cases having the diagnosis of Laennec's cirrhosis from the years 1938 to 1950 were reviewed. From these, 100 cases in which the immediate cause of death was massive gastrointestinal hemorrhage were selected for study. None of these cases had been subjected to any surgical procedures. The following data was extracted from the autopsy records: sex, age, presence or absence and size of esophageal varices, site and cause of the bleeding, the weight of the liver and spleen, the presence or absence of ascites and conditions which may have contributed to the bleeding. From these data the incidence of lesions causing death from gastrointestinal hemorrhage was determined and some of the possible clinical implications deduced.

Results

The sex and age of these cases fall into the known pattern for this type of liver disease (Tables I and II).

TABLE II

Sex Incidence

Males	75%
Females	25%

The sites of bleeding are listed in Table III. Included in the classification of gastritis was hemorrhagic gastritis, erosive gastritis, hypertrophic gastritis and gastric mucosal diapedesis.

In the group of unidentified causes no esophageal varices or other pathological lesions were found.

It is readily apparent that in this study ⅓ of the cirrhotics who died from massive gastrointestinal bleeding, did so from sources other than esophageal varices! That this may be a modest figure may be supported by the fact that when varices were present, but without perforation, and no other site of bleeding could be demonstrated, the pathologists concluded that the varices were the source of the bleeding (24 cases). Also, presumably more cases of variceal exsanguination would reach the autopsy room because of the relatively higher mortality rate in such patients as compared to other causes of gastrointestinal bleeding.

This incidence of 33 per cent may be compared with the autopsy analysis of a similar group of cirrhotics by Enquist and Gliedman who reported 29 deaths due to bleeding from lesions other than esophageal varices in their series of 85

cases—a percentage of 34.1 per cent[3]. It may also be compared with Palmer, who in his clinical study of potential bleeding lesions in cirrhotics reported an incidence of 39 per cent of lesions in addition to esophageal varices which could be responsible for gastrointestinal bleeding[4].

Gastritis was the commonest source of extravariceal bleeding, and the hemorrhagic type comprised 9 of the 12 cases in this group.

The gastric ulcers were not simple erosions but true ulcers placed in various areas of the stomach and all occurred in men.

The esophageal ulcer case had bled massively and also perforated, causing a mediastinitis, either complication being capable of being the immediate cause of death.

TABLE III

CAUSE OF FATAL GASTROINTESTINAL HEMORRHAGE IN 100 CASES OF LAENNEC'S CIRRHOSIS

Cause	No. or %
Esophageal varices	67
Perforation shown	43
Perforation not shown	24
Esophageal ulcer	1
Gastritis, hemorrhagic, etc.	12
Gastric ulcer	4
Gastric varices	2
Duodenal ulcer	3
Hemorrhagic diathesis	2
Unidentified causes	9
Summary	
Death from bleeding esophageal varices	67%
Death from bleeding other than esophageal varices	33%

Only 3 duodenal ulcers were found as the source of the bleeding. Two others were observed, but were uncomplicated. Other studies have had a similar incidence[5].

Both patients with the hemorrhagic diatheses had thrombocytopenic purpura and the gastrointestinal bleeding was diffuse.

The number of cases where necropsy failed to reveal the site of bleeding was disappointingly large, but not as compared with nationwide statistics, and suggests that postmortem autolysis may obscure some of the more subtle causes of bleeding, particularly those involving the gastric mucosa[2].

Except for cases with a hemorrhagic tendency, the data suggests that bleeding from sites distal to the duodenum is unusual.

In the patients bleeding from esophageal varices in which a defect was shown (43 cases), 33 per cent had punctate openings suggesting a mechanical rupture of the wall of the vessel, while 66 per cent had an erosive or ulcerated defect most likely attributable to acid-peptic dissolution of the vessel wall.

The data was analysed from the point of view of whether or not there might be some physical findings or combination of findings which would increase the probability of correct diagnosis of the bleeding site. It was assumed that a

TABLE IV

SOURCE OF BLEEDING IN PATIENTS WITH AND WITHOUT POSITIVE PHYSICAL FINDINGS

		Esophageal Varices		Other		Unidentified	
		No. of Cases	%	No. of Cases	%	No. of Cases	%
Hepatomegaly (2,000+ gm.)	Present	29	69	11	26	2	5
	Absent	38	66	13	22	7	12
Splenomegaly (250+ gm.)	Present	39	74	12	22	2	4
	Absent	28	59	12	26	7	15
Ascites (100+ c.c.)	Present	40	75	11	21	2	4
	Absent	27	57	13	28	7	15
Splenomegaly and ascites	Present	22	73	7	23	1	4
	Absent	45	64	17	24	8	12
Hepatomegaly and ascites	Present	14	78	4	22	0	0
	Absent	53	65	20	24	9	11
Hepatomegaly, splenomegaly and ascites	Present	6	60	4	40	0	0
	Absent	61	67	20	23	9	10
Hepatomegaly and splenomegaly	Present	10	50	8	40	2	10
	Absent	57	71	16	20	7	9
No organomegaly or ascites	Present	10	72	2	14	2	14

2,000 gm. liver and a 250 gm. spleen was the minimized sized enlargement that could be detected clinically by physical examination or radiographic means. It was further assumed that any amount of ascitic fluid over 100 c.c. could be determined or suspected clinically (Table IV).

With these qualifications close inspection of the results indicated that under no set of circumstances was there a deviation of more than 11 per cent from chance alone, in the incidence of variceal or extravariceal bleeding, as indicated in Table III. This strongly suggests that from a clinical point of view the presence of hepatomegaly, splenomegaly, ascites, or any combination of these find-

ings, or the absence of any of them individually or in any combination points no more strongly to esophageal varices, or other causes of gastrointestinal bleeding than chance alone.

From the protocol description of the caliber and extent of the esophageal veins a gradation on the basis of 0 to 4 plus was made (Table V). It was found that 91 per cent of the veins were small to moderate sized vessels. Although the exact incidence of very large (4 plus) varices in cirrhotics is not known, these data suggest that small to moderate sized varices are as susceptible as very large ones, or perhaps more so, to bleed seriously.

When bleeding occurred from sites other than esophageal varices, the latter were absent in over half of the cases (52 per cent). In 48 per cent of the cases

TABLE V

ESTIMATED SIZE OF ESOPHAGEAL VARICES CAUSING DEATH FROM HEMORRHAGE

Size (Caliber or Extent)	No. of Cases	%
1 plus (very small)	1	2
2 plus (small to moderate sized)	41	61
3 plus (moderate to large sized)	19	28
4 plus (very large)	6	9
	Cases 67	100%

esophageal varices were present but were not the source of the bleeding. In these instances they tended to be very small to moderate size (Table VI).

COMMENT

From the aforegoing it seems clear that a significant number of cirrhotics bleed from gastrointestinal causes other than esophageal varices. Further, that having established that the patient is suffering from cirrhosis of the liver, the history may suggest a source of bleeding but physical examination ordinarily does not materially help in increasing the accuracy of the diagnosis as to the bleeding site. Therefore the diagnosis must rest on accurately performed endoscopic and radiographic examinations correlated with therapeutic tests.

The urgency of establishing the diagnosis and effecting hemostasis is indicated by the fact that ⅔ of all patients dying of gastrointestinal hemorrhage do so in the first seven days of illness; and of the cirrhotics who succumb to this complication approximately 75 per cent of the cases die of progressive hepatic decompensation precipitated primarily by the blood loss anemia[6].

The safety of carefully performed upper gastrointestinal radiography in patients not in shock has been repeatedly emphasized in the literature. Emergency roentgenographic examination, however, has its diagnostic limitations. Warthin reported that in 30 per cent of their patients either no diagnosis, or an incorrect diagnosis was made by this means[7].

The identification of esophageal varices radiographically, according to the data presented (Table VI), gives the clinician no real assurance, in itself, that they are the source of bleeding. In addition the most frequent cause of bleeding other than varices is gastritis, which cannot be reliably demonstrated by roentgenography. Therefore this diagnostic means must be supplemented by esophagoscopy and gastroscopy.

TABLE VI

ESTIMATED SIZE OF ESOPHAGEAL VARICES ACCOMPANYING OTHER CAUSES OF BLEEDING

Size (Caliber or Extent)	No. of Cases	%
None present	17	52
1 plus (very small)	7	21
2 plus (small to moderate sized)	8	24
3 plus (moderate to large sized)	1	3
4 plus (very large)	0	0
	Cases 33	100%

That x-ray and endoscopic means complement each other is indicated by Palmer who reported that of 97 patients subjected to all three types of examination within the first week of illness, the diagnosis was accurately established in 94 instances. The dangers of adequate study are insignificant when compared to the hazards of therapy without knowledge of the nature of the bleeding lesion[8].

The use of the Sengstaken-Blakemore tube and tubes as described by Saydjari and others has been very helpful in many cases of bleeding cirrhotics[9]. The tubes, however, must be properly placed, with proper amounts of air in the balloons, and have proper traction, all of which must be maintained, in order for the clinician to arrive at a reliable diagnostic conclusion. These tubes are not without some risk and the positive information is limited to cases of bleeding esophageal varices. Presumptively, if bleeding is not halted with the tube, esophageal varices are not the site of the blood loss and some other cause distal to the cardioesophageal junction is present, and additional means of diagnosis must be employed.

When a patient with massive upper gastrointestinal bleeding with cirrhosis of the liver presents himself, the following plan of care is suggested: 1. Immediate hemoglobin determination and preparation for blood replacement. 2. A history, if obtainable, and general physical evaluation. 3. Placement of a tube to effect esophageal tamponade. 4. If hemostasis is effected by this means, further investigation may be performed as the physician feels necessary. 5. If the gastric aspirate continues to be bloody or if there are signs of continuing bleeding with the tube in place, emergency endoscopic examination should be performed. If endoscopy is not readily available, then x-ray examination should be performed. 6. If the radiologist sees only esophageal varices and/or finds no other cause for bleeding, endoscopic procedures are mandatory to establish the diagnosis. 7. Emergency esophagoscopic examination using local, or if necessary, general anesthesia must be performed accurately and tediously with repeated aspirations of any blood or secretions which may be present. By this means the presence or absence of esophageal varices and whether or not they are the source of the bleeding, together with the state of the esophageal mucosa may be determined. Also, gastric varices or other lesions closely adjacent to the cardioesophageal junction may be visualized. 8. If esophagoscopy does not reveal the cause of bleeding, gastroscopy may follow immediately after preparation of the gastric mucosa with an ice water lavage. 9. If the cause of bleeding escapes detection by all of these means, they should be repeated. Gastric ulcers, tumors or varices near the cardia or in the fundus, are difficult to visualize and small postbulbar, posterior duodenal ulcers may elude initial radiographic demonstration.

If the gastrointestinal bleeding stops promptly, medical management is of course continued. If, however, the bleeding recurs, or if active bleeding persists, surgical intervention must be seriously considered. The decision to subject such a patient to surgery is frequently a delicate one and requires an accurate identification of the lesion so as to facilitate the choice of operation and minimize the duration of surgery. In making this decision, it must be remembered that the immediate mortality of at least 19 per cent, and delayed mortality of over 40 per cent, in cirrhotics with continuing or recurring gastrointestinal bleeding, is a good deal higher than the fatality rate from almost any appropriate surgical procedure, with the possible exception of total gastrectomy for a diffuse hemorrhagic gastritis[7,10].

Conclusions

At least ¼ of patients with Laennec's cirrhosis who have massive gastrointestinal hemorrhage, bleed from causes other than esophageal varices; the most common of which is hemorrhagic gastritis.

The presence of hepatomegaly, splenomegaly, or ascites, or their absence gives no material aid in increasing the accuracy of the diagnosis of the bleeding site.

Esophageal varices were present in almost ½ of the cases in which bleeding was from some other source.

Emergent radiographic and endoscopic examinations are the procedures of choice and in most cases are mandatory to establish the source of bleeding.

The high immediate and delayed mortality rate in cirrhotics who are bleeding should encourage prompt and accurate diagnosis in order that appropriate medical or surgical treatment may effect hemostasis.

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ACCURACY OF SERUM PEPSINOGEN IN THE DIAGNOSIS OF DUODENAL ULCER AS COMPARED TO EWALD AND DIAGNEX TESTS*

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Definitive diagnosis of duodenal ulcer rests, ultimately, on demonstration of a mucosal defect by x-ray. In skilled hands radiologic diagnosis has an enviable record of accuracy, approaching 85 per cent according to most estimates. In the 15 per cent of patients with negative x-rays who eventually prove to have an ulcer, as shown by subsequent hemorrhage, perforation, or later x-ray visualization, other means of establishing a diagnosis earlier are needed. In such situations studies of gastric secretory function can be most helpful.

In a previous report[1] we presented a study of the comparative diagnostic accuracy in duodenal ulcer patients of gastric analysis with a standard intubation test (Ewald), and with the tubeless test (Diagnex).

Standard intubation gastric analysis as exemplified by the widely used Ewald test, provides a rough index of hydrochloric acid production, which is commonly increased in patients with duodenal ulcer. The test has three grave limitations: 1. the secretory stimulus (a carbohydrate meal) is not maximal, 2. patient discomfort is maximal, particularly in view of the fact that 3. the yield of information is relatively small. The latter is due to the fact that under the conditions of the test there is great overlap in the gastric acid secretory rates found in duodenal ulcer patients and in normals.

Table I shows the results obtained with Ewald tests in 600 patients. There were 100 patients in each of six categories based on age and sex. It can be seen that the Ewald test demonstrated hyperacidity twice as frequently in ulcer patients as in normals, in males between the ages of 50 and 80. The difference was somewhat less in the group of younger males, but it was more pronounced in the group of female patients, where hypersecretion occurred three times as often in those with duodenal ulcer as in normals. A significant number of the control patients secreted considerable quantities of acid, and overlap with the ulcer patients existed no matter which cutoff value was selected as the upper limit of normal. Vanzant's[2] study of 6,000 gastric intubation analyses (Ewald) led to a similar conclusion: although hypersecretion of acid is the rule in patients with

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duodenal ulcer, the range of normal is so great that no reading could be pathognomonic of any disease.

For both patient and medical personnel tubeless gastric analysis is more convenient than intubation tests. Many observers have documented the ability of the tubeless test to answer satisfactorily the question of whether or not the patient can secrete hydrochloric acid[3], but the test has been erratic in indicating how much acid is produced. Much serious effort has been directed to the quantitative accuracy of the test, especially in hypersecretory states such as duodenal ulcer[4,5]. A direct relationship between the amount of indicator ion excreted in the urine during a tubeless test and the mean values for aspirated acid expressed in a single figure representing both volume and concentration of acid has been described[5].

Table II summarizes our attempts to increase the diagnostic accuracy of tubeless gastric analysis by varying the time relationships between application

TABLE I

STANDARD EWALD TEST
DISCRIMINATORY ACCURACY IN DUODENAL ULCER

	% of patients with hyperacidity (over 40° free HCl)	
Group	DU	N
Males age 20-49	24	21
Males age 50-80	40	21
Females age 20-80	26	8

of the gastric secretory stimulus (caffein) and introduction of the resin bearing the indicator ion (quinine). Urine collection periods were also varied in an attempt to improve recovery of the indicator ion after its displacement from the resin by gastric acid. It can readily be seen that regardless of which test was used, hypersecretion was found approximately twice as frequently in ulcer patients as in controls.

Hypersecretion in duodenal ulcer patients involves not only hydrochloric acid but also pepsin. In 1947 Bucher's[6] review and introduction into English of the extensive earlier German work with pepsin generated a wave of interest in this enzyme which is still gaining momentum. It seeems clearly established that the chief cell of the gastric mucosa is a combined exocrine-endocrine gland which secretes pepsinogen in a ratio of 99 to 1; the bulk of the enzyme enters the gastric lumen, with 1 per cent of the output appearing in the serum, and

eventually in the urine. Urinary pepsinogen is so variable in the same individual from day to day that it seems to have no value in clinical medicine[7]. Serum pepsinogen (more accurately referred to as acid protease, since what we actually measure is the capacity of the serum to digest a protein at a very low pH), on the other hand, shows remarkable constancy for a given individual. It shows no diurnal fluctuation, and is uninfluenced by meals, emotions, or by the administration of such potent drugs as insulin, atropine or histamine[8]. The only drug reported to influence the serum pepsinogen level is ACTH, which causes a

TABLE II

MODIFICATION OF TUBELESS GASTRIC ANALYSIS
DISCRIMINATORY ACCURACY IN DUODENAL ULCER

Test modification	Number of patients		Specimen	Upper limit (excretion quinine in urine)	% of patients with hyperacidity	
	DU	N			DU	N
I Control period 1 hr. Collection at 2 and 4 hrs.	32	100	2nd hr.	200 mcg.	65	32
			4th hr.	200 mcg.	74	36
			4 hr. total	400 mcg.	70	36
II Control period 90 min. Collection at 90 min.	8	55	90 min.	150 mcg.	63	45
III Control period 90 min. Collections at 2 and 4 hrs.	41	100	2nd hr.	200 mcg.	55	46
			4th hr.	200 mcg.	70	58
			4 hr. total	400 mcg.	80	48
IV Control period 2 hrs. Collection at 1 hr.	6	21	1 hr.	150 mcg.	63	45

prompt and sustained rise[9]. The amount of pepsinogen in the serum appears to be closely correlated with the total gastric secretory mass. After total gastrectomy serum pepsinogen falls to nearly zero. The small residual acid protease activity remaining in the serum is thought to originate from either esophageal gastric glands or intestinal cathepsin. Serum pepsinogen is invariably low in patients with gastric mucosal atrophy, and a normal value militates strongly against a diagnosis of pernicious anemia.

Elevation of the serum pepsinogen level occurs in patients with renal disease and azotemia, presumably because of impaired excretion. High serum pepsinogen levels, described in patients with acute myocardial infarction, and

patients with hyperparathyroidism, have also been attributed to subtle changes in renal excretory function[8].

The most common cause for elevation in the serum pepsinogen is duodenal ulcer. Elevated values persist after activity of the ulcer subsides. In a few patients serial observations have shown the serum pepsinogen to be consistently elevated even before the clinical emergence of duodenal ulcer[10].

We performed serum pepsinogen determinations in 135 patients. The method of Mirsky[11] was employed, and normal values ranged from 150 to 450 units, as described by Spiro[12]. In the group of 51 duodenal ulcer patients 37, or 72 per cent, had serum pepsinogen values in excess of the upper limit of normal (Table III). Of 59 nonulcer patients only 20, or 34 per cent, exceeded this value. It should be noted that the nonulcer patients are not strictly "normals" since this group included many patients with functional gastrointestinal disease. Hypersecretion occurred twice as often in the duodenal ulcer patients as in the non-

TABLE III

SERUM PEPSINOGEN IN PATIENTS WITH AND WITHOUT DUODENAL ULCER

Group	Duodenal ulcer	Gastric ulcer	Hiatus hernia	"Normals"
Normal range (150-450 units per ml. serum)	12 (18%)	2	0	39 (66%)
Hypersecretion (460-1400 units per ml. serum)	37 (72%)	6	2	20 (34%)

ulcer patients. Moreover, 30 per cent of the duodenal ulcer patients gave values exceeding 700 units, and this did not occur in any of the nonulcer patients.

COMMENT

Serum pepsinogen as a parameter of gastric secretory capacity has several advantages. It requires only a single venipuncture, and is, from the patient's viewpoint, considerably more convenient than intubation. Since the serum pepsinogen shows great constancy in a given individual, a high level is helpful in detecting the "ulcer diathesis". As a reverse corollary, a low pepsinogen level is of great help in excluding duodenal ulcer from diagnostic consideration in patients with functional complaints which are suggestive of ulcer. Because of the constancy of the serum pepsinogen level, the test is of no value in indicating the state of activity or quiescence in an ulcer. This limitation is shared by studies of gastric acid in that the hypersecretion characteristic of ulcer patients typically persists during intercritical periods.

It would seem to be particularly useful in evaluating patients with suspected marginal ulcers, in whom aspiration studies are erratic because of losses of

gastric juice through the gastroenteric stoma. Another area of unique usefulness of the serum pepsinogen is in the differentiation of the cause of acute upper gastrointestinal bleeding. The serum pepsinogen will be high in the patient whose bleeding is due to duodenal ulcer, and low in the cirrhotic.

Our series did not include sufficient data for a statistically valid estimate of serum pepsinogen values in patients with gastric ulcer and gastric cancer, but the observations of others have shown that the range of secretion is so similar in the two groups that the test is of no value in distinguishing between benign and malignant gastric ulceration[12].

It would appear that in the study of patients suspected of duodenal ulcer the procurement of gastric secretory data sufficiently accurate to be diagnostically useful requires the use of one of the newer, refined intubation tests. These tests, as described by Musick[13], Roth[14], and Littman[15], have reduced the range of error in correlation of values for gastric acid secretion and the roentgen diagnosis of duodenal ulcer to 20 per cent or less. Moreover, intubation provides the opportunity for simultaneous study of acid secretion and pepsin secretion over any specified time interval, as well as the procurement of washings for cytologic study.

Conclusions

Serum pepsinogen determinations showed no greater discrimination between duodenal ulcer patients and controls than did the Ewald or Diagnex tests; hypersecretion occurred twice as frequently in the ulcer patients as in the controls. Although it is not as versatile or precise as the newer intubation gastric analyses, the serum pepsinogen test should prove valuable in the study of patients suspected of duodenal ulcer when intubation is contraindicated or refused, in patients suspected of marginal ulcer, and in the differential diagnosis of acute upper gastrointestinal bleeding.

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RECENT ADVANCES IN ROENTGENOLOGY OF THE UPPER GASTROINTESTINAL TRACT*

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The title, as listed on the program, is a little misleading, since the program chairman asked me if I would confine my remarks to lesions or situations affecting the duodenum. Other portions of the upper gastrointestinal tract have been, or will be, covered by other speakers.

In considering advances or so-called progress in the roentgenologic examination of the upper gastrointestinal tract, we should say a word or two about radiation hazard. So much has already been said in the newspapers, and otherwise, that I will dismiss it only with the remark that today no radiologist in his right mind, or gastroenterologist, either, would think of examining a patient without using a properly calibrated fluoroscope with a minimum of at least 3 mm. of aluminum filtration and wearing a lead rubber apron and lead rubber gloves.

The use of x-ray examination, including fluoroscopy, for the discovery and follow-up observation of lesions of course can be abused but, in proper hands, the method is still the medium par excellence for the disclosure of gastrointestinal disease, the newspapers notwithstanding.

I would like to say a word or two about the use of image amplifiers for fluoroscopy. Those who have used image amplifiers, and I am sure there are many of you in the audience, have learned by this time that it is impractical to attempt to do a complete gastrointestinal study with any of the presently available forms of image amplification. They have very definite advantages, but they also have some disadvantages. The radiation exposure to the patient, of course, is considerably reduced, but it is difficult to conduct a fluoroscopic examination through an ocular eyepiece or by means of a reflecting mirror, the plane of which changes as you move your head or the patient. An excellent image can be obtained, but I believe that further improvements in amplifiers are desirable before they will entirely supplant fluoroscopy done with proper visual accommodation.

I do believe that as image amplifiers are improved, cineradiography will be more generally used. It is available now, of course, but the greatest limitation of cineradiography has been the high patient dosage. When present methods which permit motion pictures with x-rays with a very minimum of radiation

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exposure are better perfected, I am sure that cineradiography will be used with increasing frequency for evaluation of the gastrointestinal tract, particularly for the study of function and the effect of surgical procedures: i.e. vagotomy and pyloroplasty. A particularly fertile field is the esophagogastric junction, which we know little enough about, and concerning which there is at present considerable confusion.

In order to evaluate the duodenal area, we must have some sort of a contrast agent, and here, in the agents that are available to us, there have been a number of improvements. The first has been in the refinement of the barium and the colloidal barium, which is now available, gives a beautiful image of the mucosal surface, which is so important. Many of the commercially prepared meals are loaded with nonopaque substances which produce confusing images. I personally feel that a mixture of colloidal barium and water, with whatever flavoring agent you or your patients wish, is as good as we have available.

The opaque solutions, such as Gastrografin or Hypaque, present some very interesting applications. In the first place they do not solidify or impact in the intestinal tract as barium may do, and therefore they permit roentgenologic procedures which, in the past, were carried out with some patient risk. We can use these opaque solutions in the acutely ill patient and in the patient soon after surgery. It is too early to evaluate observations that are under way regarding the use of these agents in the acute abdomen to determine the frequency of leakage in perforated ulcers as compared with the visualization of air. This is an interesting study.

We must not forget that both of these agents can be irritating. The stomach rebels a little against them, so it is better to administer them by a Levin tube, if possible. The patient who has had recent gastric surgery will exhibit edema around the anastomosis or surgical site and, when we superimpose an irritating substance, there are certain physiologic changes which we can expect and which we should be careful not to interpret as evidence of disease.

(Slide) On this first slide I have attempted to compare the detail of an ordinary colloidal barium meal with that of a soluble opaque medium, in this case Gastrografin. There is a difference which I would like to point out; the image of the soluble medium is less sharp and is somewhat fuzzy. None of the soluble media that I have used will cling to the mucosal surface; hence, we are dependent upon the silhouette pattern. You can rotate the patient and see an ulcer niche or deformity, but in a stomach which is partially empty, the medium will not cling to the surface of a crater and reveal it as a residual shadow.

In examining a patient for a suspected acute obstruction, we must not forget that soluble media will pass through a lesion unless the obstruction is complete. You can have a partially obstructing lesion of fair size that will transmit a soluble medium and this may be somewhat disarming.

An advantage of the soluble medium is that it progresses rather rapidly through the small bowel and frequently in two or three hours will produce a visualization of the colon.

(Slide) The next slide is that of a patient with a suspected pyloric obstruction. Gastrografin was given by a Levin tube and the roentgenogram revealed a classical pattern of pyloric obstruction, a large, dilated stomach with hyperperistalsis and a trickle of medium through the outlet. The obstruction was secondary to a large gastric ulcer which is obscured by the medium and which was shown only by profile studies. This may seem to be an exaggerated case, but I assure you that it is one of the sources of error in using opaque solutions that I have not experienced with barium.

Frequently after surgery, the surgeon will become distressed because the patient is vomiting more than he thinks he should, and he would like to have the radiologist find out why. With soluble media, there is a tendency to make these examinations earlier and earlier in such cases. This slide of a Gastrografin study shows an apparent defect at the outlet of the stomach. The patient had a duodenal ulcer for which a pyloroplasty was performed and actually, what we are seeing is the edema incident to the pyloroplasty rather than disease. The medium is passing out of the stomach adequately. The surgeon was concerned that there might be some leakage, but there was none. We must be careful not to mistake postoperative edema for real lesions. This edema, in my experience, will last at least ten days to two weeks and, in some experiences, longer, if there has been much intramural hemorrhage from the sutures.

Ulcers originating in the base of the duodenum are frequently a problem. We seem to see more of them reported in the literature. In the slide of this interesting case the lesion seems to straddle the pylorus. Actually, it is a basal duodenal ulcer and I show it because the lesion has perforated posteriorly into the pancreas. The crater, as we visualized it with the fluoroscope and in the films, was projected on the antral portion of the stomach. Many of these ulcers will have so much associated edema that it is easy to suspect that the lesion is a primary posterior wall gastric lesion that may be malignant. Many of these low lying or basal ulcers will imitate a pyloric malignancy, and sometimes only the surgeon or pathologist can make the distinction.

This is the slide of a patient who had severe hematemesis. The medium used was Gastrografin. The film shows a persistent pyloric defect and a large, irregularly rounded collection of opaque medium with a central defect which at first blush suggests a crater or something which is coated with opaque medium. In the second film of this case we can see gastric mucosa passing across the crater and part of the crater appears to be even extragastric, and that's exactly what it was. The lesion was a duodenal ulcer originating in the base of the bulb, which perforated posteriorly into the pancreas. The defect in the

central portion of the crater is a large blood clot, and we are seeing only the periphery of a large crater.

Four days after operation, the crater was reduced in size. There was a defect in the crater itself, due to a piece of muscle pledget placed over a vessel by the surgeon to help control hemorrhage.

I am sure that in following this type of patient, you would not want to use barium, and this is one of the useful applications of soluble media.

The next case is an example of the queer defects we see in the duodenal bulb associated with enlarged Brunner's glands. At first blush, they simulate a marked degree of duodenitis with edema, but the differential point, I believe, is that the changes are confined largely to the duodenal bulb. The mucosa in the second portion of the duodenum is relatively normal. It is very unusual in my experience to get much duodenitis with edema without some associated inflammatory change and at least edema in the second portion. The defects of enlarged Brunner's glands may simulate air bubbles or multiple polyps in the duodenal bulb. We not infrequently see air bubbles in the duodenal bulb when the Hampton technic is used to disclose posterior wall duodenal lesions.

Because of the cholecystographic media that are available today and the increasing efficiency of visualizing the duct system, we are becoming more interested in lesions involving the biliary ducts and the duodenum. Ulcers in the second portion of the duodenum may be obscured by the duodenal bulb, which is frequently dilated proximal to the lesion. Second portion ulcers exhibit a rather typical incisura. They are best shown when pressure is made on the horizontal portion with retrograde expression of barium. They may frequently imitate tumors of the duodenum because of associated edema. A complication of second portion ulcers is penetration into the common duct with resulting visualization of the ducts. You may see air in the ducts and identify the complication in the preliminary films without the use of opaque media.

When there is a history of bleeding, we must not let the presence of an ulcer deformity keep us from examining the rest of the duodenal loop in the search for a bleeding lesion since it is entirely possible for a patient to have two lesions, either of which, or both, may bleed.

We are seeing more and more patients who have been operated on for an abdominal aneurysm. Occasionally the graft will leak and these patients, as you know, may bleed into the gastrointestinal tract. The only sign the radiologist may observe is in the distal duodenum, where the duodenum passes the site of the aneurysm or the graft. I have learned from experience to take a long look at this area in these patients, as all you may see is a persistent extraluminal defect in filling.

Discussion

Dr. Harry A. Davis:—From a surgical viewpoint the fat malabsorption becomes quite important in patients who have had resections of the pancreatic head or total pancreatic resections, and particularly intestinal resections.

Work which has been done quite recently indicates that while the whole of the small intestine is a source of fat absorption, the major point of fat absorption seems to be the distal third of the small bowel. If you happen to have a patient who has to have a resection for some reason or other, the effects upon fat metabolism are going to be less if the resection involves the upper half or two-thirds of the small intestine rather than the lower third.

This work was done in dogs and was confirmed in rats, and probably it is also true in the human being, although to my knowledge no similar investigation has been done in the human being. On the basis of analogy it is probably similar in man.

A second point that I would like to make in regard to this paper is this: the question of fat absorption and the study of the lipid curves in the blood. I think that one must consider two factors. The height of the curve that one obtains and its rate of disappearance may be rather puzzling under different conditions unless one considers the fact that the height of the curve and the rate at which it will return to normal will depend upon two major mechanisms. One of these is the rate of absorption of the fat, and the second is the rate of removal of the fatty material from the blood.

As you can readily see, many different causes may affect each of these two major mechanisms. Therefore, it is not wise to extrapolate the height of a curve that one may obtain directly to the type of fat that one happens to use, whether it is saturated or unsaturated. In other words, if you find that a saturated fat does certain things and unsaturated fats do other things, we still have many factors which have to be taken into consideration before we can consider it simply on the basis of whether the fat is saturated or not saturated.

Question:—What are the effects of emotion on lipid levels?

Mr. H. V. Thomas:—The question was the effect of emotion on lipid levels.

In answer to the question I might say that we observed that on certain occasions, the fasting levels of several of our students would be elevated to a considerable degree above their usual fasting levels. This attracted our attention and we questioned these students discovering that these specific changes were associated with the subjects' activities prior to the experiment. Some of these activities were: lack of sleep the night before, studying for exams, or simply not going to bed at their usual time.

It was our good fortune to be able to follow these same subjects over a period of 2 to 3 years and we feel that we can safely state that stress does play a role on blood lipid levels especially that of cholesterol. We must state, however, that there were other periods when the cholesterol and fatty acid levels were increased for some unelicited reasons.

No definitive experimental studies were made to prove this concept up to the present.

Question:—"In postoperative cases fat has been found in sputum and urine yet no ill effects are noted. Please comment."

Mr. Thomas:—I must frankly state I just don't know.

Dr. Davis:—That is an interesting question. It brings up the whole question of fat embolism. As you all know, fat embolism occurs occasionally following various types of injury, particularly fractures of long bones, but it has also been found after soft tissue injury, and studies which have been done in many different types of cases indicate that it is much more frequent than we have realized previously.

In other words, in a very high percentage of patients who have had multiple soft tissue contusions or who have been subjected to surgical operation fat appears in the urine. I think that the explanation here is probably that fat emboli do occur very frequently and are in most patients very innocuous.

Dr. Stephen J. Stempien:—Thank you, Dr. Davis.

The next paper, on bleeding in liver cirrhosis, is certainly of great interest. It has interested us at the Veterans Hospital in Long Beach for quite some time, and I would like to comment on that; to say first that I would completely endorse the plan of approach that Dr. Oetting has brought up. We have had this plan at our hospital for quite some time.

The minute the patient gets into the ward, the very day that he comes in, we make a decision as to whether or not emergency endoscopy should be done. If for any reason the emergency endoscopy cannot be done or is unsuccessful, we immediately plan to get the patient in shape for early x-ray, and that usually means the very next day or the same day.

We prefer to do endoscopy to demonstrate at least the presence of esophageal varices before using esophageal tamponade. We feel that the use of tamponade so complicates the management of the patient, and is such a potential hazard that one ought to be certain that varices are present.

The other point is that on clinical and laboratory evidence one cannot make any assumptions as to the site of bleeding, and the direct objective approach is by far the most rewarding in our experience. Just to mention one case we had recently; that was a bleeder who, upon endoscopy, had varices and they were

eroded and they were bleeding, and the following morning we also had an upper gastrointestinal series on him because he was also a known duodenal ulcer patient in the past, and not only did he have an active duodenal ulcer, but at the same time he also had an active gastric ulcer on the lesser curvature, so he had three potential sources of bleeding.

Dr. Davis, would you like to comment on this paper?

Dr. Davis:—I think we are all familiar with the surgical problems associated with bleeding in this type of patient. I think this paper is very worthwhile, because it brings to our attention the fact that there are other sources of bleeding in patients who are known cirrhotics. This fact sometimes is forgotten and may lead to an erroneous type of treatment and perhaps death of the patient.

The statistics that Dr. Oetting has shown us are more or less in line with those found generally, except that some men have found a rather higher incidence of gastric and duodenal ulceration in known cirrhotics. In fact, some have found as much as 14 per cent in known cirrhotics.

There were one or two other lesions which will sometimes produce bleeding that Dr. Oetting did not mention. I refer specifically to the hiatal hernia, which will sometimes be a cause of bleeding. Secondly, there is a type of small intestinal lesion, which can be described as a velvety congestion of the mucosa of the small intestine. This will sometimes produce quite severe hemorrhage. Thirdly, the well-known Mallory-Weiss syndrome, which will also result in bleeding.

There was one point in the management that I thought might be added, namely, the use of blood volume determinations in these patients. If the facilities are available we find that a blood volume determination will very often help in determining whether or not we are giving enough blood to these patients. At times, it is difficult to know whether you are giving enough blood or whether the person is continuing to bleed.

Dr. Stempien:—Thank you, Dr. Davis.

Just one more statement. The reason we are so sold on doing emergency esophagoscopy in these patients is the fairly obvious experience that in most patients the x-ray examination frequently gives us little or no help; or at the best is equivocal for varicosities; and I am sure that we find about twice as many cirrhotics with varices by endoscopy as the radiologists find by their examination.

Dr. Oetting, would you come up and answer a few questions?

No. 1 is, "What were the two cases of hemorrhagic diathesis in the cirrhotic who succumbed?"

Dr. Henry K. Oetting:—The clinical records were not gone over, but ancillary to the necropsy report these two instances were thrombocytopenic purpuras.

Dr. Stempien:—One more question: "Of the 9 who had no demonstrable source of bleeding, how many had surgery and what was done?"

Dr. Oetting:—None of these patients had surgery.

Dr. Stempien:—Thank you.

The next paper was on serum pepsinogen and I would like to say a few words on that.

We have been interested in this enzyme primarily from an investigative point of view rather than its clinical utility, and our experience has been largely confined to the urinary excretion. The blood levels of pepsinogen, as Dr. Domz has mentioned, are fairly constant, and they are more or less a basal or homeostatic level, which depends on the one hand on the state of gastric activity, and on the other hand the rate of clearance by the renal mechanism, as well as to a lesser extent by the hepatic mechanism.

These levels, of course, are reproducible. The point about uropepsin, the enzyme in the urine, is that it is more sensitive to changes when you stimulate or depress gastric activity, so that from a point of view of trying to ascertain the effect of various medications or different experimental situations I think the uropepsin would reflect the changes better than the blood levels.

The thing to keep in mind also is that either blood levels or the urine uropepsin can be increased in other situations. In our experience, about 80 per cent of duodenal ulcer patients had elevated levels, above normal. But you can get marked elevations in hypertrophic glandular gastritis, the type that is also associated with hyperchlorhydria, and you can get marked elevations in superficial gastritis due to the so-called Block phenomenon; in other words, the enzyme output and the hydrochloric acid output may be diminished in the stomach, but the enzyme may be elevated in the bloodstream.

Emotional stress can elevate uropepsin and blood pepsinogen, and dietary factors are also important. People on high protein intake, especially high meat protein intake, will have upper normal or even above normal levels.

In my own opinion, the practical value of pepsinogen determinations is quite limited, because of the marked variations and overlapping for different groups. We do not use these tests for diagnosis. We are old-fashioned enough to rely on a simple two-hour basal HCl secretion in duodenal ulcer patients, and we use it mainly to pick out our hypersecretors among the intractable group. In that way we get an idea whether or not this patient is amenable to conventional medical therapy or will he be a failure to it.

There is a question for Dr. Domz. Would you come up, Dr. Domz?

"Is serum pepsinogen elevated equally in cases of gastric and duodenal peptic ulcer?" I think you did mention something about it, but would you comment further?

Dr. C. A. Domz:—Our series was relatively small, and the slide illustrated only eight gastric ulcers. In those patients the secretion rates were slightly above normal. This does not agree with the published studies by Mirsky and by Spiro, in which they found that blood pepsinogen levels agreed rather closely with the level of gastric acid secretion. As you know, gastric acid secretion, if you lump all gastric ulcers together is normal or low, which is contrary to the rule in duodenal ulcers.

If, however, you break gastric ulcers down into those which are low on the lesser curvature and distinguish them from those elsewhere in the stomach, those low on the lesser curvature will have high acid levels and will also have relatively high pepsinogen levels. The remainder of gastric ulcers will have below normal acid levels and will have low or normal pepsinogen levels.

Dr. Stempien:—There is one more question here, Dr. Domz: "Would serum pepsinogen levels and uropepsin determinations be of value during steroid therapy in the evaluation of developing ulcers?"

Dr. Domz:—Not enough work has been done, actually, to give a clearcut answer to this question. ACTH or steroid therapy will produce elevations in serum pepsinogen, and this will be a constant finding as long as the patient is on therapy. It would seem, based on this information, that the levels will be high whether or not the patient has an ulcer. This compares to the findings we described earlier, where a given person will have a constantly high pepsinogen level whether or not at the moment he has an active ulcer. In other words, the high serum pepsinogen level is a characteristic of his individual constitution, and may predispose him to an ulcer. So far as indicating whether or not a patient has at the moment a steroid ulcer, I don't believe the serum pepsinogen would be very useful, because it wouldn't change much. Perhaps the urinary pepsinogen levels would be, but we have had very little experience with urinary pepsinogen levels.

Dr. Stempien:—Thank you, Dr. Domz. I would certainly agree with you and simply add that our own practice is to put every patient going on steroids or ACTH automatically on a full ulcer program, regardless of whether or not he has history or complaints of peptic ulcer or what not.

The next paper for discussion is the one by Dr. Camp on x-ray of the upper gastrointestinal tract.

I would like to make a few general remarks on this paper, mainly from the point of view of the clinician rather than as posing to be any expert in radiology.

I think a few things are to be said about x-rays in general in this area. So many of us, unfortunately, are exclusively oriented about the x-ray examination, and for that reason we may sometimes be misled by a negative x-ray. I think in my own experience I have gotten into difficulties and trouble in accepting negative x-ray examinations without further ado.

The x-ray, when positive, in my opinion usually indicates fairly well advanced disease, so the x-ray, although a central part of our study, certainly should be supplemented by other studies; both laboratory and endoscopic. I think the clinician should get in the habit of looking at films himself, preferably in company with the radiologist, and I think this habit should be lifelong. Sometimes the radiologist just accidentally overlooks something; at another time even a stupid question put to him by the clinician will make him think and come up with additional suggestions about the patient.

The other thing is not to accept a fluoroscopic impression. We know that fluoroscopy can give a great deal of information on functional changes, but when the fluoroscopist mentions that he saw some static abnormality but cannot demonstrate it on film you had better have a second look.

The "second look" by x-ray is important, especially when the second look is further adopted to use some special technic or to give special attention to some areas. In our experience there are a few lesions in the upper gastrointestinal tract that are commonly overlooked by radiologists, or probably better put, not demonstrable by x-ray. Esophageal varices is one; esophagitis in its early stage is another; esophageal hiatus hernia may be difficult to demonstrate. It may be there and then it may not, and the same experience holds for endoscopy.

Gastritis, of course, is not susceptible to x-ray diagnosis, although it is frequently made. Small gastric polyps sometimes are difficult to find by x-ray, as well as small gastric ulcers, and of course a number of hemorrhagic erosions or the lesions of Weber-Osler-Rendu disease obviously would not be shown by x-ray. So we should have a broad approach to the study of the upper gastrointestinal tract.

Personally I am against the addition of an esophageal study to the stomach and duodenal study. I think a very good esophageal study ought to be done separately, and in the upper gastrointestinal study I am certainly more concerned to get good stomach examinations rather than duodenal. I know that sometimes you get the opposite—a very elaborate study of the duodenum and very poor films of the stomach. In my opinion the importance of lesions of the stomach far outweighs the importance of lesions of the duodenum.

I am not particularly unusually disturbed by missing a duodenal ulcer. I can still treat the patient. But I would like, if possible, to find an early carcinoma.

Dr. Camp, would you come up, if you have any further comments?

Dr. Camp:—I have no further comments, except I would agree with what you have said wholeheartedly. I think by the time the radiologist gets around to finding most of the lesions distal to the duodenal bulb, they are not very promising lesions for the surgeon, although I believe we are beginning to recognize them much earlier. So far as the stomach is concerned, I think that improved media, judiciously used, will improve our efficiency there. Of course, any test is only as good as the man who uses it, like your gun or your camera.

THE EFFECT OF AMBUTONIUM BROMIDE, A NEW ANTICHOLINERGIC AGENT IN ULCER THERAPY*

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Kirsner et al[1] have noted that, "anticholinergic drugs alone are inadequate in the management of peptic ulcer. They should be administered only as adjuncts to conventional treatment with antacids, diet, sedation, and other therapeutic measures".

This report is a description of the treatment of 179 patients who had symptoms of gastrointestinal diseases with a new preparation, Aludrox®SA**. Aludrox SA contains, in either tablet or liquid form, 2.5 mg. of ambutonium bromide and 8 mg. of butabarbital combined with aluminum hydroxide and magnesium hydroxide approximating one teaspoonful of aluminum hydroxide gel and one-quarter teaspoonful of milk of magnesia.

Ambutonium bromide is a potent new parasympatholytic agent which has antisecretory and spasmolytic actions, particularly on the gastrointestinal tract. Ambutonium bromide is indicated for the relief of hypersecretion and hypermotility which occur concomitantly with gastric and duodenal ulcers and other organic and functional disorders of the gastrointestinal tract.

Chemically ambutonium bromide is a quaternary ammonium compound; the chemical name and structure of which are as follows: (3-carbamoyl-3 3-diphenylpropyl)ethyldimethylammonium bromide

Pharmacology:—The parasympatholytic activity of ambutonium bromide has been studied by Hoekstra and Dickison[2]. Their *in situ* gastrointestinal studies, using dogs under pentabarbital anesthesia, demonstrated that ambutonium bromide reduced the activity of the ileum. When spasmogenic agents

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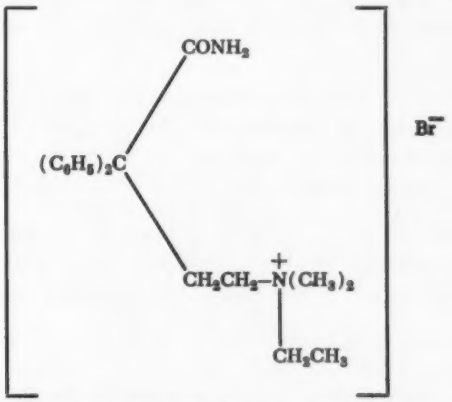
**Available from Wyeth Laboratories, Inc., Philadelphia, Pa.

were given intravenously ambutonium bromide, 1.0 mg. per kilogram given intravenously or 5 mg. per kilogram given orally, was effective in blocking the vasodepressor action of 0.2 mg. per kilogram of intravenous acetylcholine, the action of 0.05 mg. per kilogram of intravenous arecoline, and the action on salivation of 0.1 mg. per kilogram of intravenous pilocarpine. Ambutonium bromide was found to approach atropine in potency in these experiments.

The effects of ambutonium bromide on gastric ulceration, gastric secretion, and acidity in rats were studied, using the Shay technic of pyloric ligation. The 18-hour survival rates and the amount of ulceration observed in rats treated with ambutonium bromide, atropine, and other anticholinergics after pyloric ligation were compared. Ambutonium bromide afforded protection approximately equivalent to that of atropine in these experiments[3].



Chemical structure of ambutonium bromide

Acute and chronic toxicity studies in rats and dogs revealed no adverse effects after oral doses from 20 to 40 mg. per kilogram daily for a period of several months[4].

Secretion and Motility Studies

The effect of the anticholinergic drug ambutonium bromide on basal gastric secretion was studied in 40 patients who had duodenal ulcers.

The technic of basal gastric secretion tests is well known. The patient fasts for at least 12 hours and takes no medication for a full day before the test. The gastric tube is introduced into the antrum and the stomach is emptied completely. After 30 minutes, the stomach is again aspirated and the drug or placebo is given via a tube. Specimens are collected every 15 minutes for one hour before and at least 2 hours after the drug is given. Volume is measured. The

pH is determined with a Beckman pH meter and the free and total acidity are determined by titration with 0.02 N sodium hydroxide, with Topfer's reagent and phenolphthalein as indicators.

The anticholinergic drug was given in increasing doses which varied from 5 to 40 mg. A significant decrease in volume of secretion, free acidity, and total acidity was observed beginning with the 10 mg. dose. Higher doses were more effective, but caused considerable side-effects and it was the impression that the satisfactory decreases obtained with the 10 mg. dose was sufficient for clinical use, except in cases in which the acid values were inordinately high. In the latter situation, patients would, of necessity, have to employ higher doses of the anticholinergic drug. This was a personal matter, and it was found that the patient could quickly determine for himself which dosage was effective for him. Because of the combination of drugs used in Aludrox SA, an attempt was made to determine what synergistic activity, if any, the sedative might have on gastric secretion.

A one-sixth grain dose of butabarbital was found to have no appreciable effect on gastric secretion; however, with increasing doses, the degree of inhibition of the volume of gastric secretion was more marked. Unfortunately, the increased dose was too sedative for clinical use. Meprobamate (Equanil®) in 200 mg. doses was substituted for the butabarbital and, in 10 patients, a moderate degree of inhibition of volume of secretion was obtained. The combination of ambutonium bromide, 10 mg., and meprobamate, 200 mg., showed an even more impressive response and should be given further clinical trial.

Motility studies were carried out for 20 patients. Twelve of the 20 patients had the irritable colon syndrome. The remaining 8 patients had duodenal ulcers. The most dramatic responses usually occurred in the duodenal ulcer patients. There was marked hypermotility and rapid emptying time. Beginning with the 10 mg. dose of ambutonium bromide, there was moderate diminution in motility. Increasing doses of ambutonium caused more marked delay and the greatest effect was noted in the delay in evacuation of the barium column from the stomach and small bowel. There was a lesser effect on the motility of the large bowel, even with doses up to 40 mg. A similar ineffectiveness of other anticholinergic agents has been noted in the treatment of such diseases as ulcerative colitis[5]. The effectiveness of ambutonium bromide in diminishing hypermotility, so commonly found in duodenal ulcer patients and in those who have the irritable colon syndrome, is illustrated by the roentgenograms shown in Figures 1a-1d.

Because of the diminution of gastric secretion and acidity and also because of the effect of the anticholinergic on gastrointestinal tone, healing of the ulcer is usually more rapid, and the effect on pain is pronounced. Clinical improvement is often manifest within a period of from 24 to 48 hours, and roentgeno-

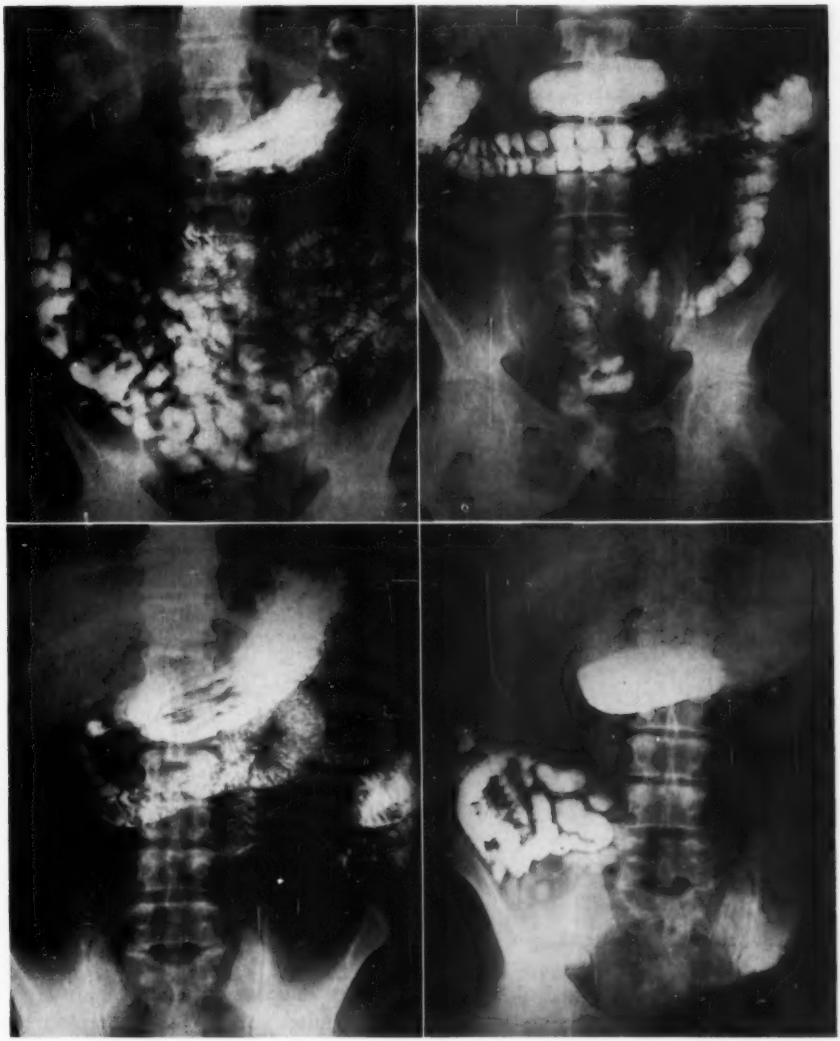


Fig. 1a—Upper left. One-half hour film depicting marked hypermotility in case of irritable bowel syndrome. Head of barium column in cecum.

Fig. 1b—Upper right. Two hour film demonstrating head of barium column in rectum in case of irritable bowel syndrome.

Fig. 1c—Lower left. One hour film demonstrating delay in motility of stomach and small bowel in case of irritable bowel syndrome after ingestion of ambutonium bromide. Head of column in jejunum. Compare with Fig. 1a.

Fig. 1d—Lower right. Five-hour film demonstrating delay in stomach and small bowel motility after ingestion of ambutonium. Head of barium column at ileocecal junction. (Compare with Fig. 1b).

grams revealed rapid healing of active ulceration (Figs. 2a and 2b and Figs. 3a and 3c).

Procedure

All 179 patients included in this study have been under constant supervision for the past 2 years. Of this group, 111 had duodenal ulcers, 10 had gastric ulcers, one had a combined gastric and duodenal ulcer, and one had a pyloric ulcer. One patient had a marginal ulcer following subtotal gastrectomy. Another

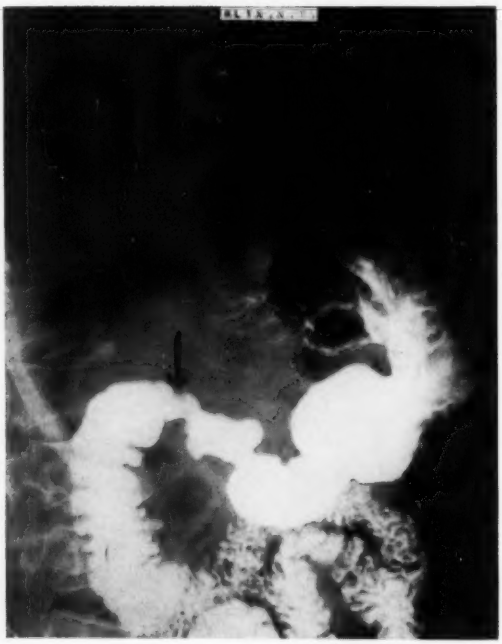


Fig. 2a—Active ulcer crater at apex of duodenal bulb before treatment with Aludrox SA.

patient who had a marginal ulcer was treated for diarrhea and severe pain after two subtotal gastrectomies and a vagotomy. Included also were 10 patients who had symptomatic hiatus hernia without ulceration but who complained of the development of heartburn after eating. Thirty-one patients who had irritable colon syndrome with abdominal pain and symptoms of constipation, or frequent soft bowel movements especially associated with states of anxiety tension, were carefully studied. Nine patients who had irritable duodenal bulb with pylorospasm also were treated because of the symptoms of vague epigastric distress, bloating after meals, and heartburn.

Complete physical examinations were done at the beginning of the treatment period and the diagnoses were established roentgenologically. Gastroscopic, esophagoscopic, and sigmoidoscopic examinations were employed, whenever indicated, to aid in the diagnoses or in the follow-up studies during therapy. Complete blood counts, including liver and kidney profiles, and urine and stool examinations also were done.

Roentgenologic examination was repeated whenever indicated, especially for the patients who had gastric ulcers. Most of the patients who had duodenal ulcers had spot films taken at the beginning and at the end of the seasonal period.

The dose of Aludrox SA prescribed varied with the individual needs of the patient and with the condition for which he was being treated. Usually, from 1

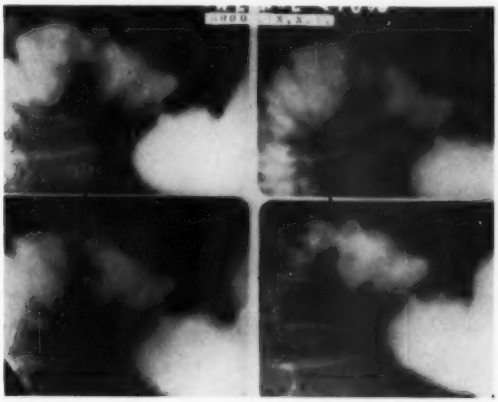


Fig. 2b—Complete healing of ulcer crater at apex of duodenal bulb after 6 weeks of treatment with Aludrox SA. Relief of symptoms was obtained within 72 hours.

to 4 drams (teaspoonfuls) of the combined form of medication, taken four times daily, were prescribed as the initial medication. For those who had more severe pain, the initial dose was increased to from 3 to 4 drams, taken four times daily. After relief was obtained, a maintenance dose of 1 or 2 drams, four times daily was prescribed. In some instances, 1 to 2 ambutonium bromide tablets (10 mg. each), taken four times daily, were substituted for the liquid preparation; one-half ounce of the aluminum hydroxide gel with magnesium hydroxide being taken separately after meals. In those instances in which the relief from tension was believed to be a very important adjuvant in the treatment, 200 mg. of meprobamate (Equanil®) were substituted for the butabarbital.

At the first sign of recurrence of symptoms, the patients were instructed to take the full therapeutic dose and to continue on full medication until the pain

was alleviated, after which time, the maintenance dose could again be taken and continued indefinitely.

Usually, the diet was only moderately restricted. It is our belief that the average patient who has an ulcer may eat what he likes as long as he eats often, drinks at least one quart of milk daily, and refrains from eating highly spiced foods or using alcohol and tobacco. For those who have the irritable colon syndrome, a bland, low residue diet was prescribed. Those patients who became constipated on this regimen were instructed to take milk of magnesia, in adequate doses, before retiring.

Fig. 3a—Acute ulcer crater in patient with 25 years' history of duodenal ulcer. Pain was very severe before treatment with Aludrox SA.

Results

Most of the patients in this study have been maintained on varying doses of the Aludrox SA mixture for the entire 2-year period. Of the 179 patients, 139 (78 per cent) obtained complete relief from symptoms; 23 (13 per cent) obtained moderate relief (Table I). Seventeen patients (10 per cent) failed to respond to therapy. The average ulcer patient obtained an adequate response on 2 drams of Aludrox SA, taken four times daily. In the group which had

milder symptoms, relief usually occurred within a period of from 24 to 48 hours. Those patients who received meprobamate (Equanil) in place of the butabarbital obtained excellent results.

Follow-up studies after treatment with Aludrox SA were made of 2 patients who had regional ileitis. One patient had had a free perforation with a resection of the right half of the colon followed by a resection of a portion of the ileum 5 years later, after the development of obstructive symptoms. Aludrox SA was prescribed because of bloating, heartburn, and diarrhea. This patient obtained

TABLE I

Results of Therapy

Disease	No. of Cases	Relief from Symptoms		
		Complete	Moderate	No Relief
1. Duodenal ulcer	111	95	10	6
2. Gastric ulcer	10	10	—	—
3. Combined gastric & duodenal ulcer	1	—	1	—
4. Pyloric ulcer	1	1	—	—
5. Gastrojejunal ulcer	1	1	—	—
6. Hiatus hernia	10	—	7	3
7. Irritable colon syndrome	31	24	4	3
8. Duodenitis	9	7	—	2
9. Regional ileitis	2	—	1	1
10. Ulcerative colitis	2	—	—	2
11. Dumping syndrome	1	1	—	—
Total	179	139	23	17
Per cent		78	13	10

poor results on 3 drams of Aludrox SA, taken four times daily, but did have less discomfort and could perform her usual household tasks. The second patient who had regional ileitis complained only of bouts of diarrhea with abdominal pain. No operative procedures were done. A state of moderate comfort was maintained on a bland diet and 2 drams of Aludrox SA, four times daily.

There were no sigmoidoscopic or roentgenologic changes, although both patients had been maintained on this medication for approximately one year.

Follow-up studies of the 111 patients who had duodenal ulcers were continued for approximately 2 years. It was possible, therefore, to observe these

patients through four ulcer seasons and, thus, evaluate the results of therapy carefully. In 95 cases, the patients have been completely relieved of their symtoms and have been able to carry on with their usual work uninterruptedly. Of the remaining 16 patients, 10 have been moderately relieved, with periods of freedom from pain lasting from season to season. When symptoms recurred, it was commonly found that the patients had failed to continue the diet or medication or both, or had returned to excessive use of tobacco or alcohol. Usually, the symptoms were promptly controlled on the administration of a slightly larger dose of medication which was continued indefinitely. In 6 cases, no relief was obtained from the medication and these cases must be classified as failures. These patients were the type which might be called the "intractable group", with penetration posteriorly into the pancreas and with no period of remission between ulcer seasons. Patients of this type usually require surgical treatment,

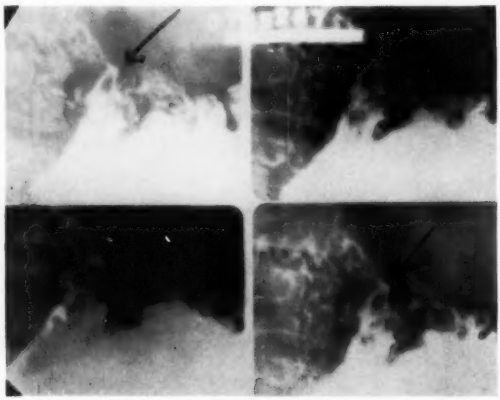


Fig. 3b—Six weeks after treatment with Aludrox SA. Crater diminished in size. Symptoms relieved after 72 hours of treatment.

or frequent hospitalization with around the clock observation and continual intragastric antacid drip or hourly antacid medication.

All the gastric ulcers studied were benign. The diagnoses were based on roentgenologic and gastroscopic observations. Both types of observations were used throughout the period of therapy until the patients were completely symptom-free and the gastric lesions were observed to be completely healed. In all instances, relief from pain was quickly obtained by the use of Aludrox SA. Constant observation during the past 24 months has not revealed any evidence of recurrence of the lesion in any case of the patients in this group.

In one case in which the patient had both gastric and duodenal ulcers the response was satisfactory and the gastric lesion was seen to be completely healed

within a period of 6 weeks. This patient, however, had a recurrence of pain 6 months later, apparently from the duodenal ulcer as roentgenologic examination failed to demonstrate a gastric lesion. Careful follow-up of this patient is being continued and, as of this date, there appears to be a remission of symptoms.

A young woman had symptoms of severe abdominal pain and vomiting. Roentgenograms (Figs. 4a-4c) showed an acute pyloric ulcer. A dramatic response was obtained by the use of a bland diet and 3 drams of Aludrox SA, four times daily. Relief from pain was achieved within 48 hours and the ulcer crater was no longer visible on roentgenologic examination 6 weeks later.

In one patient who was a chronic alcoholic, chronic relapsing pancreatitis and cyst formation developed. After resection of two large cysts, the patient began to hemorrhage from the gastrointestinal tract. The stomach was resected

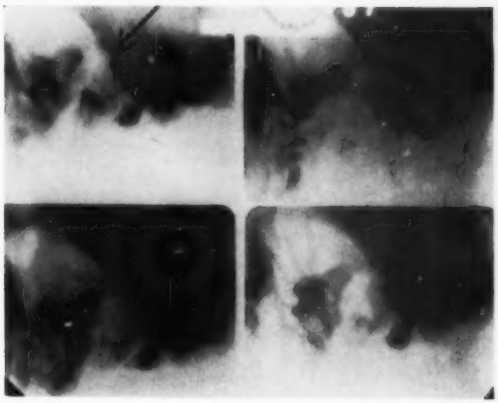


Fig. 3c—Complete healing of acute exacerbation of chronic duodenal ulcer after 8 weeks of therapy with Aludrox SA.

and the patient recovered. The patient, however, reverted to his previous alcoholic habit and, approximately one year later, a large marginal ulcer developed. Four drams of Aludrox SA, taken four times daily, an ulcer diet, interdiction of alcohol, and bed rest were prescribed. Within a period of 8 weeks, the ulcer was completely healed (Figs. 5a and 5b).

Another patient in whom there was perforation of the duodenal ulcer had a simple purse string suture in 1950. The ulcer perforated again in 1951 and a subtotal gastrectomy was done in 1955. A marginal ulcer developed 8 months later and a revision resection with vagotomy was performed. The present symptoms were those of "dumping syndrome" and constant diarrhea (6 to 8 bowel movements daily). Four drams of Aludrox SA, four times daily, were prescribed; the diarrhea was quickly controlled. The "dumping syndrome" symptoms gradu-

ally disappeared after several weeks and, to date, the patient has remained symptom-free on a maintenance dose of one dram of Aludrox SA, four times daily.

The diagnosis of irritable colon was made for 31 patients. Complete roentgenologic and sigmoidoscopic examinations failed to reveal any organic lesion; however, spasm of the descending colon, splenic flexure dilation, or both, and an easily palpable, tender, descending colon were revealed in most instances on physical examination. These patients were taught to recognize the relationship of their abdominal complaints to periods of increased tension. Twenty-four patients have been completely relieved by the use of Aludrox SA, the doses varying with the severity of their symptoms. At the onset of therapy, most of these patients were given 1 or 2 drams of Aludrox SA, four times daily, for

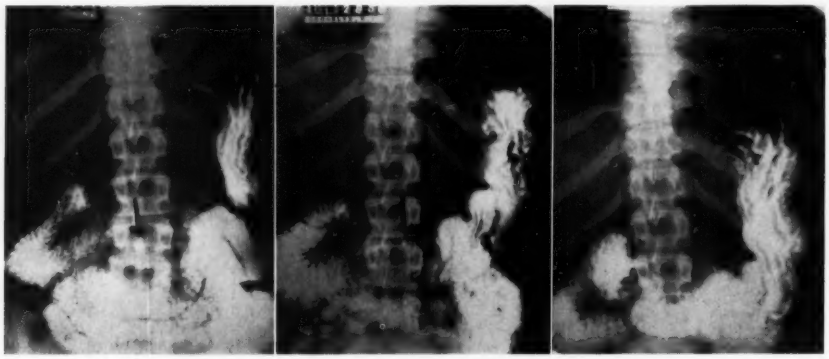


Fig. 4a Fig. 4b Fig. 4c

Fig. 4a—Acute pyloroduodenal ulcer before treatment with Aludrox SA. Relief of pain was achieved within 48 hours after institution of therapy with Aludrox SA.
Fig. 4b—Considerable diminution in size of acute pyloroduodenal ulcer 4 weeks after treatment with Aludrox SA.
Fig. 4c—Complete healing of acute pyloroduodenal ulcer 6 weeks after treatment with Aludrox SA.

approximately one week. With the amelioration of symptoms, the dose was changed to a PRN basis. Because of the obvious psychogenic background, most of these patients must be maintained on the PRN basis until they can learn to cope with their individual problems. Several of these patients who are under psychiatric treatment, are on maintenance doses of Aludrox SA.

A very difficult group to treat included 10 patients who had hiatus hernia of the paraesophageal type. The most distressing complaints were heartburn, bloating after meals, and moderate to mild epigastric pain. The ages of these patients varied from 58 to 75 years. Surgical intervention was not advocated in

any instance because complications such as ulceration, melena, hematemesis, or intractable distress were not encountered. These patients usually were advised to remain on a bland ulcer diet. A low caloric diet was prescribed for obese patients. The patients were also warned not to wear constricting garments or to do heavy lifting. They were also instructed to sleep with the head elevated. The Aludrox SA was given approximately one hour after meals, and before retiring. Of the 10 patients, 7 reported moderate improvement of symptoms. The remaining 3 patients were not improved until the amount of the drug prescribed was increased to the point at which sedation was obtained. These patients have been taking this medication continuously but most of them found the night dose to be the most important, and vary the dose from 1 to 3 drams as required.

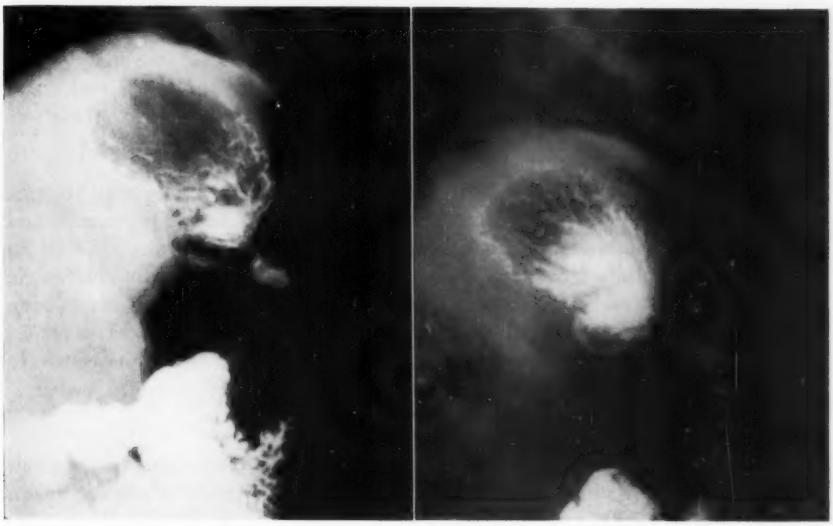


Fig. 5a Fig. 5b

Fig. 5a—Huge gastrojejunal ulcer before treatment with Aludrox SA.
Fig. 5b—Complete healing of gastrojejunal ulcer after 8 weeks of treatment with Aludrox SA.

Nine patients for whom a diagnosis of "duodenitis" was made were treated with Aludrox SA and meprobamate. Their symptoms were considered to be purely functional. Seven of the 9 patients obtained complete relief. Two patients were obviously severe psychoneurotics and were advised to have psychiatric therapy when medical therapy was unavailing.

To date, neither blood nor liver disturbance has been encountered as a result of the medication which the patients received. The average dose of the anticholinergic, when taken alone, was 10 mg., administered four times daily. In combination with the antacid and the sedative, however, the ambutonium

was found to be effective in one-half the amount and, thereby, made it possible to obviate some of the disagreeable side-effects so often seen with the use of the higher doses of an anticholinergic agent. Although it was not possible to eliminate such side-effects as dryness of the mouth, moderate visual blurring, slowing of the urinary effort in males, and constipation, it was not necessary to curtail the drug in any instance because of the aforementioned side-effects. In most instances, the side-effects were only disturbing to the patient for the first few days or for as long as one week after institution of therapy. After that time, there were no longer any complaints and it was possible to continue the combined medication for 2 years without any serious disturbing results.

Summary and Conclusion

Complete or partial remission of symptoms associated with peptic ulcer or other "irritable" gastrointestinal disease was obtained in 162 (91 per cent) of 179 patients by the use of ambutonium bromide, aluminum hydroxide gel with magnesium hydroxide, and butabarbital, administered separately or in combination, and either in solution or in tablet form.

The average dose of the anticholinergic, when taken alone, was 10 mg., administered four times daily; however, in combination with the antacid and the sedative, the ambutonium bromide was often found to be quite effective in half the aforementioned doses. The reduction in the amount of anticholinergic used was instrumental in obviating some of the disagreeable side-effects seen with the use of larger doses. Side-effects which did occur lasted for a period of from 1 day to 1 week at most and, not in one instance was it necessary to discontinue the medication because of side-effects. No evidence of blood dyscrasia or hepatic dysfunction has been observed.

When the sedative effect of butabarbital was a problem, but the patient still required control of an emotional condition, the substitution of meprobamate, 200 mg., was adequate and the results were very satisfying; in fact, the combination of ambutonium, 10 mg., and the meprobamate, 200 mg., showed an even more impressive response which merits further clinical trial.

The anticholinergic properties of ambutonium bromide have been adequately determined by studies of gastric acidity and by roentgenologic studies of motility. A significant decrease in volume of secretion free acidity, and total acidity was observed beginning with the 10 mg. dose of ambutonium bromide. The motility studies showed the most dramatic response to be found in the duodenal ulcer patients who had very marked hypermotility and rapid emptying time. There was moderate diminution in motility on the 10 mg. dose of ambutonium; with increased doses, there was a more marked delay, the greatest effect being noted in the delay in evacuation of the barium column from the stomach and small bowel.

Because of the diminution of gastric secretion and acidity and the effect of the ambutonium bromide on gastrointestinal tone, healing of the ulcers was more rapid, and the effect on pain was quite pronounced. It was not unusual to see clinical improvement within 24 to 48 hours after institution of therapy.

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THE SYSTEMIC IMPORTANCE OF RELATIVE LIVER DYSFUNCTION TO THE DEVELOPMENT AND SPECIFIC TREATMENT OF VASCULAR AND BLOOD DISEASES*

A Review of Ten Years of Investigation

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Canajoharie, N. Y.

During the last ten years, vascular and blood diseases have increased markedly. Greater efforts than ever are made to solve the problem of preventing and successfully treating these serious conditions. The purpose of this paper is to explain the basic role which relative liver dysfunction plays in the development and specific treatment of these diseases.

Function, Dysfunction and Condition

Applied to an organ, the medical term "function" denotes the performance of an action. Three fundamental degrees are possible: normofunction, hyperfunction and hypofunction. A "healthy" person will offer normofunction of his organs. In case of disease, they will develop relative dysfunction in form of hyperfunction or hypofunction.

In contrast, a condition is a state of shorter or longer duration. The normal condition of an organ indicates the constant performance of all functions which are required of it. Its state could change if more actions have to be performed. Such a situation will develop when disease strikes the human body. An organ may be able to comply readily with the hyperfunction which illness demands of it; then, it will not undergo any changes of its condition. In serious diseases, when hyperfunction changes to hypofunction, it may be left in a different state, i.e. condition after the sickness has run its course.

Turning to the liver, its function is directed by the hypothalamic region, the center of the autonomic nervous system. It has to coordinate all impulses in such a way as to maintain the inner balance of the human organism. The degree of the liver function is determined by the anatomical condition of the liver tissue and its neurohormonal regulation which depends on the productive efficacy of two organs closely related to the liver: the spleen and the pancreas.

Pronor® and Liver Function

Proof for this assertion is offered by Pronor®, an intramuscular injection, consisting of liver and spleen extract with insulin. This drug will bring about an independent action of the liver by stimulating the hypothalamic region. Then, the liver would react by elaborating certain autosubstances—if they are needed.

*Read before the Section on Gastroenterology at the 35th Anniversary Congress of the Pan American Medical Association, Mexico City, 7 May 1960.

As described in another paper[1], they are the blood proteins which are synthesized in the liver. The Blood Protein Test (BPT) was developed on this basis. It uses rapid changes of the serum globulin and the albumin/globulin ratio for the evaluation of the results. Studies by other investigators[2-5] have fully confirmed this test which states whether the liver function is normal or abnormal.

Hepatoendothelial and Hepatoepithelial System (HNS-HPS)

Ten years ago, a paper[6] was published introducing the hepatoendothelial and hepatoepithelial systems (HNS-HPS). It was explained that the HNS comprises the endothelial parts of the liver, spleen and bone marrow while the HPS consists of the epithelial parts of the liver, stomach, pancreas and intestinal tract. Later on, the adrenal gland was added to the systems[7]. On this basis, it is possible to correlate the HNS-HPS, the blood proteins and the blood cells with different vascular and blood diseases. The following scheme is self-explanatory.

TABLE I

Systemic Connections			Diseases caused by		
Hepatic systems	Blood proteins	Blood cells	Hepatic hyperfunction	Hepatic normofunction	Hepatic hypofunction
HNS	Fibrinogen	Platelets	Phlebitis thrombosis	none	Hemorrhagic tendency
HPS	Albumin	Erythrocytes	*Polycythemia vera*	none	Anemia (aplastic anemia)
HNS	Globulin	Leucocytes	Leukemia	none	Leukopenia (Agranulocytosis)

This scheme is based on the fact that a normal liver condition indicates a normal HNS and HPS which are responsible for normal values of the blood proteins and the blood cells. If they remain within the normal range, vascular or blood diseases will not develop. The values of the fibrinogen fraction, e.g., run from 0.2 to 0.4 gm. per cent with an average of 0.3 gm. per cent. The platelets have a normal range from 200,000 to 400,000/cu.mm. with an average of 300,000/cu.mm. All these figures can increase or decrease in pathological cases. Thus, the fibrinogen can be reported in traces only or to the amount of 1.5 gm. per cent, i.e. within the pathological range. The same changes can occur in the serum proteins, the erythrocytes and the leucocytes. If such a situation arises, clinical symptoms will develop permitting the diagnosis of specific diseases. According to the above offered scheme, their basic cause is relative liver dysfunction, either hyperfunction or hypofunction. The correctness of this statement would only be proved if a treatment could be offered which normalizes liver dysfunction and at the same time improves the disease which is its symptom.

Pronor and Treatment of Liver Diseases

Published papers[8,9] and communications from other investigators[2,10,11] have reported the remarkable results which have been obtained with Pronor as a therapeutic agent*. It has proved to be a specific treatment for diseases of the liver and related organs. It is important to point to the fact that the exclusive action of Pronor in such cases is the stimulation of an independent liver function. Careful observations for over more than ten years have convincingly shown that relative dysfunction of the liver affecting the HNS and HPS will interfere with the synthesis of the blood proteins especially when a larger amount of them is urgently needed. This situation was already expressed as follows[1]: "We live on albumin, we stop bleeding with fibrinogen, we fight for our lives with all three globulin fractions and finally we die of our incapability of synthesizing more plasma proteins."

Evidence will be submitted that Pronor is a specific treatment for thrombophlebitis, phlebothrombosis, hemorrhagic disorders, *polycythemia vera* and leukopenia. Leukemia will not be discussed since it represents a special problem. But considered theoretically, it is to be expected that Pronor compounded with cortisone acetate[9] could be used as successful physiologic therapy for this serious disease.

Thrombophlebitis and Phlebothrombosis

Numerous papers and books have been published dealing with the etiology of thrombophlebitis and phlebothrombosis. Blood coagulation has been extensively studied and the investigations have revealed that it is a complex process in which many factors participate. The three blood proteins AC globulin, fibrinogen and prothrombin are some of them. They are exclusively synthesized in the liver. Platelets, another factor, are formed in the bone marrow. Splenic disorders influence their number.

Since the hepatoendothelial system consists of the endothelial parts of the liver, spleen and bone marrow, the function of the HNS must be abnormal or vascular diseases could not develop. In many cases, this relative dysfunction does not seem to be caused by severe liver cell damage since a microscopic examination of the hepatic tissue will not offer pathologic findings. But there must be a cause and it can only be the relative deficiency of the three substances contained in Pronor. When they are supplied by intramuscular injection, the hypothalamic region is stimulated. Then, relative liver dysfunction—may it be hyper- or hypofunction—will begin to revert to as normal a liver function as the hepatic condition will permit while the patient will improve at the same time.

*For reasons beyond the control of the author, Pronor® is not yet commercially available but it can be obtained for clinical investigations through him.

The rapid action of Pronor in the human body is demonstrated by the results of the Blood Protein Test[1]. According to this test, the liver function is normal when the blood proteins are determined before the injection of 1 c.c. of Pronor and the albumin/globulin ratio (within its normal range 1.3-3) does not change at all or by less than 5 per cent of its value after one hour and two hours. The following cases are reported as further information on this test.

Case 1:—M.F., male, age 33 years. Diagnosis, duodenal ulcer*. Confirmed by x-ray examination. Liver, enlarged by one fingerbreadth, painful to touch.

TABLE II

Case 1	Total blood proteins gm. %	Fibrinogen gm. %	Serum albumin gm. %	Serum globulin gm. %	A/G ratio
Before injection	7.0	0.43	4.36	2.21	1.97
One hour later	6.83	0.53	4.12	2.18	1.88
Two hours later	7.13	0.89	4.46	1.78	2.50
After treatment of 10 days	6.18	0.24	4.22	1.72	2.45

Result:—Relative liver dysfunction. Function markedly affected. Fibrinogen fraction increased by 100 per cent two hours after injection. After 10 daily injections of Pronor, it was within the normal range. Patient had considerably improved (Table II).

Case 2:—E.S., male, age 47 years. Diagnosis, moderately advanced liver cirrhosis. Liver, enlarged by two fingerbreadths. Spleen, palpable.

TABLE III

Case 2	Total blood proteins gm. %	Fibrinogen gm. %	Serum albumin gm. %	Serum globulin gm. %	A/G ratio
Before injection	6.63	0.50	4.33	1.84	2.40
One hour later	6.63	0.81	4.48	1.34	3.34
Two hours later	6.43	0.43	4.50	1.50	3.00

Result:—Relative liver dysfunction. Function moderately affected. Fibrinogen increases above normal range after one hour but is within normal range after two hours (Table III).

*It is the author's opinion that peptic ulcer is caused by liver dysfunction.

Case 3:—F.P., female, age 67 years. Diagnosis, viral hepatitis. Liver, enlarged by two fingerbreadths, painful to touch.

TABLE IV

Case 3	Total blood proteins gm. %	Fibrinogen gm. %	Serum albumin gm. %	Serum globulin gm. %	A/G ratio
Before injection	7.66	1.03	3.40	3.23	1.05
One hour later	9.25	1.13	3.98	4.14	0.96
Two hours later	8.35	1.07	3.97	3.31	1.20

Result:—Relative liver dysfunction. Function is critically affected. Fibrinogen within pathological range. No change (Table IV).

Case 4:—R.M., male, age 34 years. Diagnosis, duodenal ulcer. Confirmed by x-ray examination. Liver, palpable and painful to touch.

TABLE V

Case 4	Total blood proteins gm. %	Fibrinogen gm. %	Serum albumin gm. %	Serum globulin gm. %	A/G ratio
Before injection	6.92	0.60	3.37	2.95	1.14
One hour later	5.38	0.77	3.48	1.13	3.07
Two hours later	6.26	0.33	3.73	2.20	1.69

Result:—Relative liver dysfunction. Function moderately affected. Fibrinogen still within pathological range after one hour, but within normal range after two hours (Table V).

These results which speak for themselves prove that rapid changes of the blood proteins take place after the intramuscular injection of 1 c.c. of Pronor. The objection could now arise that the blood proteins are labile and as previously reported[1] will change by themselves as required by the human body. They could be determined three times within two hours and the results could be used for a liver function test.

Such an assertion would be contrary to the fact that hepatic normofunction depends on the sufficient supply of specific substances from the liver itself, the spleen and the pancreas. Since it cannot be ascertained which of these organs fails to deliver its proper amount in case of disease, Pronor is to supply all of them. With the administered injection, the situation is compelled to change

because the hypothalamic region is stimulated and the liver function, so far only dependent on the organs related to the liver, will now be transformed into an independent function. It is only this function which can provide the basis for a physiologic liver function test. It must be emphasized that not only the blood proteins but any other substances synthesized in the liver can be tested by the same method and will then provide reliable information on other hepatic functions. This fact makes the Blood Protein Test an all-comprehensive liver function test.

The treatment of thrombophlebitis and phlebothrombosis can only have one ultimate aim: to dissolve the thrombus and restore normal circulation in the obstructed blood vessel without any side-effects whatever to the patient. It was already mentioned that Pronor is a specific therapeutic agent for vascular diseases. The following case reports are offered as proof.

Case 5:—R.D., female, factory worker, age 46 years. The patient was examined for the first time on 2 February 1953. Her past history revealed that at age 10, she had an operation for peritonitis from a perforated appendix. At age 44, a hysterectomy and appendectomy were performed. She complained of stomach distress, hyperacidity and flatulence.

The patient was a tall woman who weighed 172 lbs. Her blood pressure was 172/93. Her abdomen was extremely distended. The liver was enlarged by one fingerbreadth and sore to touch. The gallbladder was tender. The spleen was palpable. The impression was that the patient suffered from liver dysfunction and cholecystopathy.

On 21 August 1954, the patient came to the office at 8 P.M. The day before, she had been on a trip and had driven a car for two hours and a half. During the following night, she developed pain above the right medial malleolus but she was again behind the wheel in the afternoon for three hours. While driving, swelling, redness and severe soreness developed in the affected area of the right leg. It ached from there up to the hip making it nearly impossible for her to use it.

The examination revealed that the pulse was 86 and the blood pressure 182/100. The temperature was 99.4. The liver was enlarged by one fingerbreadth and sore to touch; the spleen was palpable. The area above the right medial malleolus was swollen and red. The long saphenous vein could be felt as a hard cord which was very sore to slightest touch. A diagnosis of acute thrombophlebitis was made and 1 c.c. of Pronor was administered. The patient was advised to return home—she lived six miles from the office—and to arrange for a home call the next day if her condition should not improve. The next evening, she appeared on crutches at the office and related that she had noticed less pain two hours after the injection. After another hour, the pain had practically stopped. She could sleep well and had an uneventful night. During the day, she had felt good because the pain was negligible. The area above the right

medial malleolus was very slightly swollen. Redness had changed to a pink color and the soreness had nearly cleared up. The hard vein had turned soft. The pain in the right leg including the hip had disappeared which was the first symptom of improvement. The patient received the second injection of 1 c.c. of Pronor.

On 26 August 1954, after five injections, the following note was entered on the record, "Patient is in excellent condition. She has no complaints. The area above and around the right medial malleolus is normal and is no more painful to touch. Temperature, 98°. Blood pressure, 162/90".

The daily injections of Pronor were continued. On 28 August 1954, the patient discarded the crutches and started to walk without support. A slight swelling of the right foot developed which had cleared up the next day.

Until 18 September 1954, the patient received 14 injections of Pronor. The right leg was completely normal, there was no swelling, no redness and no pain.

Since the patient was not hospitalized, laboratory tests were only run on 8 September 1954. The results were as follows: Erythrocytes, 4.4 million; hemoglobin, 13 gm.; leucocytes, 6,000 with 56 per cent lymphocytes; blood sugar, 104 mg. per cent; total serum proteins, 7.2 gm. per cent; serum albumin, 4.7 gm. per cent; serum globulin, 2.5 gm. per cent and the A/G ratio, 1.880.

This patient, suffering from hepatic hyperfunction, developed an attack of acute thrombophlebitis of the right leg. She was exclusively treated with Pronor at the office and the acute phase had subsided after 24 hours. After seven injections, she started to walk around again but the treatment of the relative hepatic dysfunction was continued until 14 injections had been administered. The normal laboratory reports confirmed the improvement of the hepatic function. The patient was re-examined on 28 October 1954 and the right leg was found to be in normal condition.

Case 6:—T.P., male, factory worker, age 64 years, was seen for the first time on 3 September 1957. According to his past history, he had suffered from frequent attacks of acute tonsillitis since 1951 for which he had received about 50 injections of penicillin. In March 1954, a tonsillectomy was performed. In 1953, he had severe thrombophlebitis of the left long saphenous vein. A sympathetic nerve block was done while he was hospitalized for one month. In 1956, he had thrombophlebitis of the left lower leg. In April 1957, he underwent a hemorrhoidectomy.

On 26 November 1957, the patient awoke with a "sore lump" in the right inguinal area. During the day, the "lump" and soreness increased. There was no nausea, no vomiting.

The examination revealed a medium-sized, older man who looked apprehensive. The size and sounds of his heart were normal. The pulse was 80, reg-

ular and the blood pressure was 140/80. The temperature was 98.2. The abdomen was distended. The liver was enlarged by one fingerbreadth and sore to touch. In the right inguinal area was a slightly fluctuating swelling, the size of a small plum. It could not be moved and was sore to touch. The impression was that the patient suffered from a partially strangulated hernia. He was hospitalized and referred to a surgeon who agreed to this opinion. The operation disclosed, however, that the true condition was acute thrombophlebitis of the right superficial epigastric vein which was excised.

A few days after his return from the hospital, the patient who was taking an anticoagulant, complained of a swelling in the incision and in the medial aspect of the left thigh where soreness had developed. There also was a hard swelling (7 cm.:5 cm.) above the pubic region. The examination revealed that the medial third of the left long saphenous vein was hard, swollen and sore to touch. The protuberance turned out to be a large hematoma. The liver was enlarged by one fingerbreadth and sore to touch. The coagulation time (capillary tube method, normal 3′ to 7′) was 3′45″.

The anticoagulant was discontinued and the patient received the first injection of 1 c.c. of Pronor. The next day, 17 December 1957, he had slightly improved. The left long saphenous vein was less hard and the hematoma was smaller in size. After the second injection of Pronor, the patient felt much better. The left long saphenous vein was softer and less sore. The hematoma above the pubic area was considerably reduced, especially the knob-like swelling. The liver was nearly normal in size. On 21 December 1957, he was doing rather well. The left long saphenous vein was almost normal, the swelling in the incision had flattened out and the large hematoma above the pubic region was reduced by two-thirds. The liver was normal in size.

Daily injections of Pronor were continued until 10 January 1958. On that day, the total serum proteins were 7.4 gm. per cent; the serum albumin, 4.6 gm. per cent; the serum globulin, 2.8 gm. per cent and the A/G ratio, 1.643. The serum bilirubin amounted to 0.25 mg. per cent and the coagulation time was 4′15″. The left leg did not offer any symptoms of thrombophlebitis. But the patient complained of intermittent stiffness and hardness of the left thigh and slight swelling of the left lower leg and the left foot. This condition improved, however, and he returned to work on 20 January 1958. Four days later, the coagulation time was 4′30″.

From then on, the patient was carefully watched for symptoms of thrombophlebitis but none ever developed. His coagulation time ranged from 3′30″ to 4′15″. On 4 May 1959, the erythrocytes were 4.5 million; the hemoglobin was 13.3 gm.; the leucocytes were 10,100 and the blood sugar 104 mg. per cent. The total serum proteins were 7.2 gm. per cent; the serum albumin, 4.2 gm. per cent; the serum globulin, 3 gm. per cent. The A/G ratio was 1.400 and the serum bilirubin 0.25 mg. per cent. The coagulation time was 3′45″.

From 16 December 1957 to 6 July 1959, the patient received 79 injections of Pronor for therapeutic and prophylactic purposes. The last examination on 6 July 1959 revealed that he was doing well.

This chronically ill patient suffered from three attacks of severe thrombophlebitis, the last time in both legs. After his return from the hospital, the anticoagulant was discontinued and he was exclusively treated with Pronor at the office. He was able to return to work, to drive his car and even to take longer trips. His coagulation time is within the normal range and with adequate supervision, it is expected to remain that way.

Case 7:—T.B., male, age 26 years, a farmer, was seen at the office for the first time on 15 November 1951. The tall, young man, weight 196.5 lbs., was treated for acute bronchitis. In March, 1954, he had an accident to his left hand requiring seven injections of penicillin. On 14 June 1955, he noticed a sore spot at the medial aspect of the right thigh, one handbreadth below Poupart's ligament. The sharply demarcated area was swollen, red and sore to touch. There were no chills but malaise, the temperature was 99.6. The next day, the patient ran a fever of 102.0. The red area had increased in size and acute erysipelas was diagnosed. He was given 400,000 units of penicillin. Twenty-four hours later, the erysipelas had improved but in its area, the right long saphenous vein was swollen, hard and sore to touch. Now, the diagnosis was acute thrombophlebitis. On 18 June 1955, the patient received the first injection of Pronor. The next day, he felt better. The vein was less swollen, softer and the temperature was 98.4. Until 27 June 1958, he was given six injections. The thrombophlebitis of the right long saphenous vein had fully cleared up. The patient was back to his hard work as farmer and he did not have to return for further treatment.

Case 8:—J.R., female, age 55 years, house wife and store clerk, weight: 152 lbs. The patient, a taller, pale looking woman, was examined on 6 November 1954. She had a thyroidectomy in 1949. She claimed to have been anemic for years. Her last menstruation was in March, 1954. She was treated for symptoms of the menopausal syndrome.

When seen again on 5 September 1956, the patient complained of "jabbing pain" in the medial aspect of the left lower leg which was red and swollen around the ankle joint and above it. The left long saphenous vein could be felt as a hard cord and was painful to slightest touch. The liver was enlarged by one fingerbreadth and painful. Acute thrombophlebitis was diagnosed and the patient had the first injection of Pronor. She felt better the same night and the next day, the vein was softer and barely painful to touch. The redness had nearly cleared up. On 7 September 1956, the swelling and redness were gone. The patient returned to work. Altogether, she had received nine injections of Pronor. On 10 September 1956, the laboratory reports were as follows: erythrocytes, 4.6 million; hemoglobin, 14 gm.; leucocytes, 14,500; blood sugar 104 mg.

per cent; total serum proteins, 8.5 gm. per cent; serum albumin, 5 gm. per cent; serum globulin, 3.5 gm. per cent and the A/G ratio 1.428. van den Bergh direct and indirect, negative.

Case 9:—D.B., female, retired factory worker, age 74 years, weight, 159 lbs. The medium-sized, slightly obese patient had been treated for hypertension for ten years. Her blood pressure had ranged from 180/100 to 220/140. When examined on 23 June 1958, she complained of a swelling of the left lower leg and severe pain from the second left toe to above the left ankle joint. The left long saphenous vein was felt as a hard cord from the *dorsum pedis* to the middle of the tibia. The vein was very sore to touch; the blood pressure was 210/120. The liver was palpable and tender. The patient was treated for acute thrombophlebitis. Pronor was administered. The next day, the left lower leg was barely swollen but pain persisted along the left tibia. After three injections, the patient had improved more. The left lower leg was normal and the left long saphenous vein was barely sore. After eight injections, she was doing well. There was no swelling or soreness of the left lower leg. The thrombophlebitis was cured. On 14 July 1958, she was examined again and the left leg was found to be normal. On 4 August 1959, the same findings were elicited.

As already stated, Pronor is also a specific agent for the treatment of phlebothrombosis and can even be used with good results in embolism. The following reports of two cases should prove this statement.

Case 10:—E.J., female, factory worker, age 63 years, was examined for the first time on 16 June 1948. Her past history revealed that the varicose veins of the left leg had been treated with injections.

The tall, well developed woman who weighed 182 lbs. suffered from hypertension and a large cystocele.

The patient was referred to a gynecologist who did a colpoplasty on 2 September 1948. Four days later, she developed an acute phlebothrombosis of the left leg. At her request, she was discharged from the hospital on 22 September 1948. The next day, she was seen at her home. She complained that the left leg felt like lead and that there was a "ring-like" pressure around the left thigh. The examination revealed the blood pressure to be 125/85. The left leg was swollen by 2.5" and sore to touch, the skin looked shiny. The temperature was 99.4.

On 24 September 1948, the patient was given the first injection of Pronor. Twenty-four hours later, the "ring-like" pressure around the left thigh was relieved but the swelling of the left leg was unchanged. After four injections the temperature was 98.4. The left thigh was normal while the left lower leg was still swollen. After daily injections for eight days, the patient was out of bed. The whole left leg had fully recovered. There was no swelling, no pain. The temperature had remained normal. The patient was examined again 20 days

later. Her blood pressure was 145/90 and the left leg was in good condition. She returned to work 11 days later.

Case 11:—M.C., female, widow, age 69 years, was examined for the first time at her farm home on 4 October 1951. She had a long past history of arthritis, pyelitis and an operation for varicose veins. The tall patient weighing 200 lbs., was treated for acute bronchitis. Since then, she was regularly seen at her home or the office. With a slow increase of her weight by 55 lbs., she developed hypertension but with proper medication and advice, she held her own rather well.

On 10 March 1957, the patient slipped on the floor while doing housework and fractured both malleoli of the left ankle joint. She was hospitalized; an orthopedist reduced the fractures and applied a cast to the left lower leg. When union of the left fibula did not take place he later used a pin for this fracture. Thus, the patient had two full anesthesias. When discharged from the hospital, she did not return to the farm but to her daughter's home. She was examined again on 3 June 1957. She claimed to have had a "cold" for two weeks and ran a fever of 100.0. The examination revealed that the heart was enlarged to both sides; the sounds were distant, the pulse was 88, irregular and hard and the blood pressure was 170/90. Moist rales were heard over both lungs. There was a productive cough and the phlegm was white. The patient also complained of pain in the medial aspect of the right upper abdominal quadrant. The abdomen was distended. The liver was enlarged by two fingerbreadths and sore to touch.

On 10 June 1957, the patient still coughed but the yellowish phlegm now contained bright red blood. She complained of pain in the right aspect of the chest and increased pain in the right upper abdominal quadrant. Crepitant rales were heard over the right lower posterior lobe. The liver was still enlarged and sore to slightest touch. The temperature was 102.0. Mesenteric thrombosis with embolism to the lower posterior lobe of the right lung and beginning pneumonia was the diagonsis. The patient refused to be hospitalized again and was treated at her daughter's home. She received the first injection of Pronor. During the night, she was short of breath and toward morning, she perspired profusely. The temperature dropped from 102.0 to 99.0 at 8 A.M. but rose again to 102.8. The patient had less abdominal pain. The spleen was now palpable and tender. Pneumonia had fully developed and sulfadiazine with Vitamin B-complex were prescribed. In a week—after seven injections of Pronor—the patient had improved. Only a few crepitant rales were heard over the right lower posterior lobe, the cough had decreased and less phlegm without blood was raised. The liver and spleen were normal in size. The pain in the medial aspect of the right upper abdominal quadrant had cleared up. For the first time, the temperature was 99.3 at 5 P.M. On 29 June 1957, after 14 injections of Pronor, the patient was doing well. She ate better and sat in a wheel chair. The pulse was 76, the blood pressure 150/90. There was little cough, no phlegm

and no pain. A very few crepitant rales were heard over the lower posterior lobe of the right lung. Three days later, the patient returned to her farm home. She felt fine. Since then, repeated re-examinations revealed that she had overcome this serious episode without any harmful after effects.

Hemorrhagic Tendency

As the above offered scheme indicates, hepatic hypofunction is held responsible for the development of the tendency of abnormal bleeding. Then, the conclusion can be drawn that with the normalization of the liver function this tendency should be normalized too. The following two cases should help to prove this statement.

Case 12:—A.K., male, factory worker, age 55 years, was examined for the first time on 18 July 1957. His past history revealed that he always had a tendency to abnormal bleeding. He was considered to be a "bleeder". He never had major surgery or serious internal diseases. Once, he was to undergo an operation on his nose and was in the operating room. He was given an injection, started to bleed profusely and the operation had to be cancelled. His mother was a diabetic for years; she died of a cerebral hemorrhage. His father, at age 78, was alive and still working on his farm.

During the winter 1956/57, the patient had an attack of grippe for which he had received many penicillin injections and tetracycline hydrochloride. They caused serious side-effects and he was sick for six weeks. He complained of general malaise, a "cold", headaches by spells and chronic fatigue.

The tall patient, weight 165 lbs., looked older than his age. The conjuntivae were injected and the mucosa of the nasal passages was red and swollen as was that of the throat. The outlines and the sounds of the heart were normal, the pulse was 72, regular and the blood pressure was 140/80. The abdomen was distended. The liver was enlarged by one fingerbreadth and tender to touch. The spleen was normal. A diagnosis of liver dysfunction and allergic rhinitis was made.

On 8 August 1957, the patient had five teeth extracted. He appeared at the office after he had profusely bled for two hours. He was given 1 c.c. of Pronor, also calcium gluconate and Vitamin K tablets.

When he returned to the office on 20 January 1958, he complained of the same symptoms as the first time and also stomach distress. He related that he had a tooth with a granuloma extracted two weeks before but he had only bled normally. He also emphasized that the bleeding had promptly stopped after he had been treated on 8 August 1957.

Since his liver was still enlarged and tender to touch, several laboratory tests were run; these and later reports were as shown in Table VI.

The table explains the change from the tendency to abnormal bleeding to a normal condition. On 23 January 1958, the patient had a coagulation time of 6'15" and the A/G ratio was 1.402. Therefore, he suffered from hepatic hypofunction (see Table I) involving the factors of the coagulation process. After one month of treatment with Pronor, it had decreased to 4'15" and the A/G ratio had increased to 2.083 indicating a normofunction of the HNS. The HPS was never affected since the serum albumin and the red blood count were within the normal range.

The patient was treated with Pronor. He received 30 injections in 55 days. The size of his liver was normal after 18 injections. He returned to work on 27 February 1958. On 22 May 1958, he had four teeth extracted and again he did

TABLE VI

Date	Coagulation time	Erythrocytes	Hemoglobin	Total serum proteins gm. %	Serum albumin gm. %	Serum globulin gm. %	A/G ratio	Serum bilirubin mg. %	Blood sugar mg. %	Bleeding time
1/23/58	6'15"	4.5 mill.	13.3 gm.	7.40	4.35	3.05	1.402	2.3	100	
1/31/58	5'15"			8.00	5.60	2.40	2.330	0.8		
2/7/58	4'15"			7.40	5.00	2.40	2.083	0.4		
3/21/58	3'30"			7.60	5.20	2.40	2.326		104	2'30"
4/23/58	3'45"	4.6 mill.	14 gm.	6.80	4.80	2.00	2.400	0.25	100	
5/8/58	3'45"			6.80	4.50	2.30	1.956			
12/1/58	4'30"	4.6 mill.	14 gm.	6.60	4.35	2.25	1.955		100	

not hemorrhage. On 14 March 1959, he was reexamined and his liver was found to be normal.

A second case of a patient suffering from a hemorrhagic condition was briefly reported[2] as follows, "80-year old woman. Diagnosis: Far advanced arteriosclerosis. Hepatosplenomegaly with severe hemorrhages from esophageal varices. At the height of the crisis Pronor was administered. A general improvement was the result. The hemorrhages stopped and the blood count improved. With this treatment, the patient who received 150 injections of Pronor, had only minor complaints and lived for another three years."

Polycythemia Vera

According to the offered scheme, this disease is caused by hepatic hyperfunction. There was, however, never a chance of treating such a case at the office. But it is interesting to quote the following report of a physician[11] who administered Pronor for *polycythemia vera*.

"The case of *polycythemia vera*, I gave Pronor. It is now four months and she has no more thromboses. Her blood count and hematocrit are recovering and down without further phlebotomies. Her blood pressure is down which could not be affected by medicaments prior to Pronor therapy."

Anemia (Aplastic Anemia) and Leukopenia (Agranulocytosis)

The true cause of these serious blood diseases must be attributed to relative hepatic dysfunction in the form of hypofunction. In a paper on agranulocytosis[12], the case of a 60-year old woman was reported who fell acutely ill and whose white blood count offered only 72 cells of which 8 were polymorphnuclear neutrophils, 60 lymphocytes and 4 monocytes. She made a rapid recovery with Pronor. After five days of exclusive treatment with the injection, she had 3,900 leucocytes with 36 per cent polymorphnuclear neutrophils. From the careful observation of this case evolved the conception of the HNS which stimulated the development of the HPS.

The following case of aplastic anemia with agranulocytosis was reported[2] as follows.

"Female patient. Was intensively treated with x-rays for an unusual disease which defied all attempts at a specific diagnosis. Some months later, anemia, leukopenia, diarrhea and general weakness developed. After blood transfusions only slight improvement. Patient was sent from Guayaquil, Ecuador, S. A., to well known clinics in the U.S.A. where in each of them the diagnosis of aplastic anemia was made. Patient returned as a hopeless case to Guayaquil. Now, the blood count offered severe anemia, 1,200 leucocytes with 99 per cent lymphocytes. From then on, patient was treated with Pronor, 1 c.c. twice daily. After four weeks, the erythrocytes had increased to 3,600,000 and the leucocytes to 3,300 with 50 per cent granulocytes".

Comments and Conclusions

Topographic anatomy of the upper abdomen teaches that the splenic and pancreatic veins drain the blood from the spleen, part of the stomach and the pancreas. This blood of special quality flows through the portal vein into the liver. Such a hormone as insulin from the pancreas and other specific substances from the spleen are carried to the liver for the purpose of establishing and preserving its normal function. For different reasons, one of the correlated organs may be unable to deliver one or more of the substances which are constantly needed. Then, the normofunction of the liver may change to hyperfunction and if the relative deficiency continues, hypofunction may finally ensue.

On this foundation, Pronor was developed and when it is injected it supplies the human body with those substances which are needed for the stimulation of an independent liver function. Pronor relieves a relative deficiency of

internal secretion and in that way restores the liver to normofunction provided the hepatic tissue is still able to perform these functions.

It is a well established fact that every human being is one specific entity. There is not another one exactly like him living on this planet. These great differences are obvious in laboratory reports. They are given by ranges running from a higher to a lower figure. The average figure is considered to be normal and only if they are above or below the normal range are they pathologic.

This fact explains why Pronor can be successfully used to treat such apparently diverse conditions as phlebothrombosis and hemorrhages or polycythemia and aplastic anemia. It cannot be emphasized too often that Pronor relieves symptoms which are considered to be independent diseases but are in fact only symptoms of relative hepatic dysfunction. With restored normofunction of the liver, the low coagulation time of 3′ can be increased to 4′30″ and the high coagulation time of 7′ can be reduced to 5′15″. On the one hand, there is thrombophlebitis or phlebothrombosis caused by thrombi which are quickly dissolved by Pronor, on the other hand, there is a hemorrhage which is stopped by reduction of the coagulation time. The cause of these symptomatic diseases is relative liver dysfunction which must be normalized by Pronor in order to relieve the symptoms.

Based on extensive experience during the last ten years, cases of relative hepatic dysfunction have at least doubled and this trend continues unabatedly. The cause of this deplorable situation lies in the modern mode of living which was already described in another paper[1].

"The food which is consumed is not pure anymore. The meat comes from animals which have excessively grown on feed enriched with antibiotics or on injections of sex hormones. The vegetables and fruits have been sprayed with poisonous substances. Many foodstuffs are processed and stored for many months and they do not have by far the nutritional value of even a quarter of a century ago. The introduction of potent drugs, such as the sulfa drugs, the antibiotics, the concentrated vitamins and the histamines—to name only a few—, the abuse of alcohol and nicotine, especially by women, the very early inoculations against communicable diseases, all these unnatural changes have left and still leave their detrimental marks on the human body especially affecting the liver".

Since this trend is bound to continue, relative liver dysfunction should be diagnosed and treated before serious complications have developed.

Summary

Relative liver dysfunction is considered to be the basic cause of the development of vascular and blood diseases. Pronor, an intramuscular injection con-

sisting of liver and spleen extract with insulin, is offered as a specific treatment for these diseases.

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THE USE OF BILE ACIDS AND PANCREATIC ENZYME SUBSTITUTES IN THE TREATMENT OF "FUNCTIONAL INDIGESTION"

J. ALFRED RIDER, M.D., Ph.D.*

San Francisco, Calif.

Complaints of gastrointestinal flatulence, bloating, abdominal discomfort, and heartburn after ingestion of a large meal are very frequently heard in a gastrointestinal clinic and are more common in older patients than in younger patients. Since gastric acidity tends to decrease with age, it has been postulated that biliary flow and digestive enzymes, particularly those provided by the pancreas, might also be decreased in older patients, thus decreasing their ability to digest foods.

It is very difficult to make an objective study of the ability of a patient to digest carbohydrates, fats, and proteins. Some individuals, for example, may tolerate a low fat or a low protein diet without difficulty, while if these foods are increased abnormalities of digestion may be manifested.

It was the purpose of this study to attempt to determine whether patients with a diagnosis of "functional intestinal disturbance", confirmed by roentgenograms indicating that the esophagus, stomach, duodenum, gallbladder, and colon are normal, and by the presence of normal levels of fecal nitrogen and fat have, instead, a true organic disturbance in digestive enzymes.

Materials and Methods

Twenty-two patients, 12 males and 10 females, were studied. The ages of the females ranged from 32 to 63 years, 5 being below 50 years and 5 above 50 years. The ages of the males ranged from 30 to 67 years, 4 being below 50 years and 8 above the age of 50. In addition to having roentgenograms of the gastrointestinal tract showing no abnormality, results of routine blood counts and urinalyses were normal. Gastric analysis in each case revealed the presence of free hydrochloric acid. An analysis of stools passed during a period of 72 hours indicated amounts of fecal nitrogen and fat were normal in all patients. Previous to the study patients had been prescribed a bland diet and phenobarbital, .016 gm., and belladonna, .008 gm., one tablet 4 times a day, but had experienced no relief from symptoms. The patients continued the same program during the study, except that their diets were changed so that they contained 250 gm. of carbohydrate, 100 gm. of fat, and 100 gm. of protein. Their symptoms were carefully recorded over a 2- to 3-week period, and at the end of this time each patient presented all stools passed during a 72-hour period to the laboratory for analysis of fecal fat and nitrogen. These stools were collected in large cardboard

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cartons. Each stool collection was weighed and then homogenized in a Waring Blendor. Aliquots of the stools were analyzed to determine total fat content, according to the method of van de Kamer, Huinink, and Weyers[1], and were reported as grams per cent dry weight. (The normal values are 7-27 gm.) Similar aliquots were analyzed for fecal nitrogen, as described by Hawk, Oser, and

TABLE I

AVERAGE FECAL FAT AND NITROGEN EXCRETED DURING A 72-HOUR PERIOD BEFORE AND DURING DOXEGEST® THERAPY

Patients	Number	Nitrogen (gm. in 72 hours)		Fat (gm. % dry weight)	
		Before therapy	During therapy	Before therapy	During therapy
Female over 50 years	5	6.31	4.25	16.9	13.7
Female under 50 years	5	4.62	5.67	14.0	16.3
Average		5.47	4.46	15.5	15.0
Male over 50 years	8	5.73	6.01	17.1	20.6
Male under 50 years	4	5.73	5.69	13.4	15.6
Average		5.73	5.85	15.3	18.1
Male and female over 50 years	13	5.95	5.32	17.0	18.0
Male and female under 50 years	9	5.25	5.76	13.7	16.4
Average		5.60	5.55	15.4	17.2
Total Average	22	5.64	5.51	15.7	17.2
Male and female Placebo	11	5.36		16.5	

Summerson[2]. (The normal fecal nitrogen range is from 1.5 to 7.5 gm. per 72-hour period.)

After this control period the diet was continued, and all patients took 2 tablets of Doxegest®* immediately following each meal and at bedtime.

*We are grateful to the George A. Breon Company for supplying Doxegest® for this study.

One tablet of Doxegest® contains the following:

Ketocholanic acid	12.5 mg.
Desoxycholic acid	32.5 mg.
Betain hydrochloride	65.0 mg.
Papain	15.0 mg.
Pancreatin (3X) (equivalent to 262.5 mg. N.F.X.)	87.5 mg.
Hemicellulose	25.0 mg.

TABLE II

RESULTS OF TREATMENT WITH DOXEGEST®
10 FEMALES

Patient	Age	Clinical diagnosis	Results
1.	44	Functional bowel distress	Excellent; helped her "where nothing has for 20 years"; more regular stools
2.	63	" " "	Excellent; bowels move well, marked relief of abdominal pain
3.	62	" " "	Good; relieved diarrhea, gas and bloating; could now eat lettuce and celery
4.	56	" " "	Good; relieved diarrhea and abdominal cramps
5.	57	" " "	Good; diarrhea relieved, less gas
6.	48	" " "	Good; less diarrhea, gained weight
7.	49	" " "	Good; less gas; less abdominal distress
8.	49	" " "	Good; relief of constipation and abdominal pain
9.	67	" " "	Fair; some relief of diarrhea and intestinal cramps
10.	32	" " "	Fair; less diarrhea

The patients were seen at regular intervals of 1 to 3 weeks, and their symptoms were carefully recorded and evaluated. After 3 weeks or more, another collection of stools passed during a 72-hour period was analyzed. Ten patients received placebos, either before or after the treatment program, and their symptoms were evaluated in a similar manner.

TABLE III

RESULTS OF TREATMENT WITH DOXEGEST®
12 MALES

Patient	Age	Clinical diagnosis	Results
1.	30	Functional bowel distress; nausea	Excellent; relief of nausea and abdominal pain
2.	54	Functional bowel distress	Excellent; able to digest food
3.	57	" " "	Excellent; without Doxegest indigestion returned
4.	45	" " "	Good; relief of abdominal pain
5.	67	" " "	Good; Doxegest improves digestion; less gas
6.	65	" " "	Good; relieved of constipation
7.	38	" " "	Fair; less epigastric burning
8.	45	" " "	Fair; some relief of epigastric distress
9.	64	" " "	No relief
10.	56	" " "	No relief
11.	56	" " "	No relief
12.	62	" " "	No relief

RESULTS

The results are considered in two categories: 1. Laboratory findings: a comparison of fecal nitrogen and fecal fat before and after treatment, and 2. clinical evaluation: subjective results obtained in the treatment of 22 patients.

Laboratory findings:—Table I gives the average values of the fecal nitrogen and fat for males and females. It has been constructed to show values in patients above and below the age of 50 years.

It is readily apparent that there is no significant difference between males and females in the control levels of fecal nitrogen, regardless of age, and no significant difference in the fecal fat levels. During Doxegest administration it was found that the nitrogen level was slightly lower in those females who were over the age of 50, whereas in the females under the age of 50 there was a slight increase in the nitrogen level. These figures, however, do not appear to be significant.

During Doxegest therapy there was a slight increase in fecal fat excretion in all patients except females over the age of 50 years. The significance of these figures is questionable. It is of course possible that a more definite trend would be established if Doxegest were given in larger quantities. Values in the 10 patients taking placebos were similar to the figures of patients taking Doxegest, both before therapy and during therapy.

Clinical evaluation:—The subjective results were evaluated on the basis of relief from symptoms. The patients were classified arbitrarily as having excellent results if there was immediate and complete relief from symptoms; good if there was improvement, but some symptoms were still present; fair if there was slight improvement; and no effect if there was no relief from symptoms.

In the 5 females above the age of 50 years, the results were as follows: 1—excellent, 3—good, and 1—fair. In the group of 5 females below the age of 50 years, results were identical (Table II).

Twelve males were evaluated in a similar manner (Table III). In the 8 above the age of 50, 2 had excellent results, 2 good results, and in 4 patients no effect was noted. In the 4 males below 50 years of age, the results were as follows: 1—excellent, 1—good, and 2—fair.

Summary and Conclusions

Stools collected for a 72-hour period during Doxegest therapy were compared to control collections. There appears to be no objective evidence that Doxegest causes any change in the excretion of fat or nitrogen. Clinically, however, of 10 females treated for periods of 3 weeks to 6 months, 2 had excellent results, 6 had good effect, and 2 had no effect. The age of the patient appeared to be insignificant in the clinical results.

Of 12 males who were treated for periods of 3 weeks to 12 months, 3 had excellent results, 3 had good results, and 2 had fair results. Four patients experienced no effect.

The placebos which were given to 10 patients who had reported some benefit from Doxegest therapy gave "no effect" in 8, fair results in one, and good results in one.

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THE EFFECTIVENESS OF X-PREP AS A BOWEL EVACUANT PRIOR TO ROENTGENOGRAPHY OF THE GASTROINTESTINAL TRACT

ARTHUR J. STATMAN, M.D.*

Newark, N. J.

Roentgen examination is one of the most important aids in the diagnosis of disorders of the gastrointestinal tract. But despite its importance, roentgenography, of course, is not an infallible diagnostic procedure. Lesions may be undiscernible to even those with great skill and extensive experience, and gastrointestinal films can be misinterpreted because of incomplete evacuation, gas formation, or laxative residue remaining in the bowel. Consequently all procedures related to the barium-enema and preparation of the colon for x-ray visualization should receive particular attention in order to make roentgenography as useful as possible.

The reliability and diagnostic value of roentgen studies can be enhanced by the use of an evacuant that will effectively cleanse the bowel with a minimum of irritation, gas formation or cramps; and that will eliminate such artifacts as simulated false polyps. These considerations prompted a study of a new agent, X-Prep†.

X-Prep is a bowel evacuant consisting of cocoa-flavored powder containing the total active constituent of *Cassia acutifolia* (pod senna) without irritating resins.

This paper summarizes the results of a clinical study of X-Prep in 103 patients who were referred for roentgenography of the gastrointestinal tract.

Method

There were 103 patients in the study group—males and females whose ages ranged from 17 to 70 years—all of whom suffered from functional and organic diseases of the gastrointestinal tract. The contents of a single ¾ oz. cannister of X-Prep was administered in a glass of milk or water to each patient at 4 P.M. on the day prior to roentgenographic examination. A light supper of tea, toast, and jam, and stewed fruit was allowed about two hours later. Patients were instructed to omit breakfast and return to the office early the following morning for study‡. Each of the patients was questioned on the morning of the examination as to the presence or absence of cramps, nausea, vomiting, and as to the palatability of the agent. In addition, careful observations were made regarding the quality of the films obtained and the cleansing effects of the catharsis.

*Assistant Physician, Newark Beth Israel Hospital.

†Supplied by Gray Pharmaceutical Company, New York, N. Y.

‡No further preparation such as enemas or cathartics were used.

Results

Results were classified according to the quality of visualization, the presence or absence of side-effects, and patient reaction to the palatability of the agents.

According to these criteria (Table I) X-Prep produced complete evacuation and excellent visualization in 96 patients (93 per cent) and good results in 7 patients (7 per cent). No patient experienced a poor result and none of the films was unsatisfactory. Catharsis in all cases was complete and no stool was noted in the lower bowel. Eighty-three patients (81 per cent) were completely free of cramps; mild but transient cramps developed in only 20 patients (19 per cent). The films of 96 patients (93 per cent) were free of gas formation; and insignificant gas was noted in the films of 7 patients (7 per cent). No nausea, vomiting, or other side-effects were observed in any of the patients. All the patients considered X-Prep to be highly palatable, and they readily accepted this agent.

TABLE I

Results of the Use of X-Prep in 103 Patients

Visualization	
Excellent	96 (93%)
Good	7 (7%)
Cramps	
None	83 (81%)
Slight	20 (19%)
Gas formation evident in films	
None	96 (93%)
Insignificant	7 (7%)

Comment

Thorough cleansing is the first requisite, of course, in obtaining clear, diagnostic x-ray films of the bowel. Other agents previously used in my practice also produced clear visualizations but with limitations that were not noted in this study with X-Prep. With castor oil and other laxatives, for example, a high percentage of patients complain of severe cramps and show signs of anxiety in anticipation of the procedure[1]. By contrast, because side-effects are insignificant with X-Prep and only affect a relatively small percentage of the patients, use of this agent helps ease the anxiety most patients experience. Thus the doctor can be confident that no feces or oil droplets and little if any gas remain in the colon to complicate interpretation of the films[2,3]. Since repeated examinations and serial films are frequently necessary, the confidence the doctor can feel in the accuracy of his films, may be readily appreciated.

In addition, the palatable cocoa-flavor of this agent greatly enhances patient acceptability. Aversion to such other agents as castor oil is so great that patient

cooperation may be affected adversely. By meeting with greater patient acceptance, X-Prep greatly improves the patient's attitude toward the barium-enema procedure and facilitates his cooperation. In the close patient-physician relationship attending roentgenography of the gastrointestinal tract, this benefit is substantial.

Summary

X-Prep was used as a bowel evacuant preparatory to roentgen study of the gastrointestinal tract in 103 patients. The preparation was administered in a glass of milk or water at 4 P.M. on the day prior to examination. Film visualization was excellent in 93 per cent of the cases. Side-effects were insignificant and transitory. All the patients accepted the X-Prep and several commented favorably about its palatable cocoa flavor. The catharsis was complete in all cases and there was no evidence of irritation of the colon. On the basis of my clinical experience with the use of castor oil and other evacuants, X-Prep had definite advantages. Oil droplet residue was avoided, only minimal gas was formed and cramps were not a problem, thereby enhancing patient acceptance and cooperation. By affording excellent visualization, minimal side-effects, and improved patient cooperation, X-Prep proved to be a highly effective and safe preparatory bowel evacuant for roentgen procedures.

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NEWS NOTES

Course in Postgraduate Gastroenterology

The American College of Gastroenterology announces that its Annual Course in Postgraduate Gastroenterology will be given at the Bellevue-Stratford Hotel in Philadelphia, Pa., on 27, 28, 29 October 1960.

The faculty for the Course will be drawn from the medical schools in and around Philadelphia. The subject matter to be covered in the Course, from a medical as well as surgical viewpoint, will be essentially, the advances in diagnosis and treatment of gastrointestinal diseases and a comprehensive discussion of diseases of the mouth, esophagus, stomach, pancreas, spleen, liver and gallbladder, colon and rectum. There will be a clinical session at the Albert Einstein Medical Center and again this year, in addition to individual papers, there will be panel discussions and CPC's of interest.

For further information and enrollment write to the American College of Gastroenterology, 33 West 60th Street, New York 23, N. Y.

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INTESTINES

TUMORS OF THE SMALL INTESTINE: R. Clement Darling and Claude E. Welch. New England J. Med. 260:397 (26 Feb.), 1959.

The 132 tumors in patients subjected to operation were classified into five large pathological groups. Forty-six patients (35 per cent of the total) had benign neoplasms, 33 (25 per cent) had cancer, 29 (22 per cent) had primary malignant lymphoma of the small intestine, 15 (11 per cent) had carcinoid tumors, and 9 (7 per cent) had sarcoma of nonlymphomatous origin.

One hundred and thirteen of the patients who had operations performed had symptoms referable to the tumor. The major clinical patterns were those of intestinal obstruction (67 per cent), intestinal bleeding (53 per cent), an abdominal mass (31 per cent), or perforation (11 per cent). Rare symptoms included the deficiency syndrome, the carcinoid syndrome or the signs of Peutz-Jeghers disease, or of multiple neurofibromatosis.

The obstructive symptoms that occurred were dependent on the location of the tumor as well as on its growth characteristics. Acute angulation of the bowel was most characteristic of carcinoid tumors and less so of primary malignant lymphomas. When intussusception occurred it was usually associated with a benign lesion. When intestinal bleeding occurred, it was usually of an occult nature and not with a grossly black or bloody stool. Intestinal bleeding was frequent with carcinoma, lymphoma, and leiomyosarcoma, but rare with carcinoids.

A palpable abdominal mass in the absence of intussusception was suggestive for a malignant lesion. When perforation occurred, it almost always was associated with a malignant lymphoma or sarcoma.

There seemed to be a predisposition concerned with the development of primary malignant neoplasms. Thus, inch for inch, the duodenum was by far the most frequent site of cancer. Cancer of the jejunum was much more common than cancer of the ileum, and the disease was commonly located within 30 cm. of the ligament of Treitz. On the other hand, malignant lymphoma, leiomyosarcoma and carcinoid tumors were most common in the distal ileum.

Forty-six benign tumors were treated, without mortality. These tumors are classified in 5 major groups—adenomas, lipomas, myomas, fibromas, and angiomas. Symptoms were produced in only 28 cases. Primary small-bowel malignant tumors were present in 86 cases, and symptomatic in all but 1. In order of frequency they included carcinoma, malignant lymphoma, carcinoids and leiomyosarcoma. In the 54 patients

with malignant lesions who had resections for cure before 1 January 1953, 16 (30 per cent) died postoperatively; 47 per cent of the survivors of resection for cure were living and free of disease five years later.

Certain points were emphasized of practical clinical significance; tumors found incidentally at laparotomy were nearly always benign; obstruction was usually chronic and remittent (when acute small-bowel obstruction is due to intussusception in adults, a tumor of the intestine is involved in about half the cases, and the lesion usually was benign); intestinal bleeding was common with all tumors except carcinoids, in which it was encountered in only 13 per cent of the cases in this series; a palpable mass nearly always indicated a malignant tumor (when the mass was tender a lymphoma should be suspected); perforation was common with lymphoma and sarcoma (it was rare with cancer and was not encountered with carcinoid or benign tumors).

The correct preoperative diagnosis was made in 84 per cent of the patients who had a roentgenologic study of the small intestine.

This article was most comprehensive and covered the subject excellently from a practical, clinical standpoint.

MORTON SCHWARTZ

PAIN: CARDIAC OR GASTROINTESTINAL?: Edward S. Orgain. Am. Pract. & Digest. Treat. 10:236 (Feb.), 1959.

Thoracic and upper abdominal pain occurs in visceral disease and also in cardiovascular pathology. Visceral disease produces pain of a deepseated nature, poorly localized and less intense than cardiac disease.

The enzyme tests, glutamic transaminse and lactic dehydrogenase will differentiate between myocardial infarction and pulmonary embolism, pericarditis, cholelithiasis, hiatus hernia or peptic ulcer.

X-ray is helpful to demonstrate heart configuration, aneurysms, hiatus hernia and peptic ulcer.

The electrocardiogram properly used indicates myocardial infarction it must be taken after the exercise test; ST segment depression with T-wave alteration indicates coronary insufficiency, this pain can be relieved by nitroglycerine; characteristic Q waves with ST segment elevation and T-wave inversion means coronary infarction; S waves in L-1, Q waves in L-3 and inverted T-waves in V-1, 2 and 3 often show in pulmonary embolism.

Slight alteration in ST segment or T-waves are nonspecific, frequently found in cholelithiasis, pancreatitis, hiatus hernia and must be expected because viscerocardiac reflexes cause changes in coronary blood flow and rhythm in presence of gastrointestinal pathology.

Pain from pulmonary hypertension can be relieved by oxygen and aminophylin, never by nitroglycerine.

Nitroglycerine or warm milk will relieve pain of esophageal spasm.

Splenic flexure syndrome pain usually disappears when flatus passes.

When acute pericarditis is present the cardiogram will produce characteristic ST-T waves but never Q waves.

Dissecting aneurysm may be confused with coronary infarction or gastrointestinal disease, but no electrocardiographic changes occur, unless the aneurysm causes coronary insufficiency. Palpation of the femorals, carotids or brachials will show deranged pulsations.

The pain of biliary colic appears in the upper right quadrant, normally, but when it begins in the midgastrium and radiates upward substernally, coronary disease must be suspected, as both often coexist.

Perforation of peptic ulcer or acute pancreatitis usually can be diagnosed from the history and the use of serum lipase or amylase tests on the blood.

J. EDWARD BROWN

RETROPERITONEAL HEMORRHAGE IN NONPENETRATING ABDOMINAL TRAUMA: William H. Kastl. Med. Times 87:164 (Feb.), 1959.

It is interesting to note that hematuria was found in four of the five cases reviewed by one author; variable degrees of shock as well as fever was present. There was some constancy of paralytic ileus as well as abdominal tenderness and pain in

each case.

The author feels that not infrequently some degree of hemorrhage in the retroperitoneal space occurs in nonpenetrating abdominal injuries and that if one keeps this in mind, the proper diagnosis can be arrived at. In such cases, he recommends that scout films of the abdomen be made in order to rule out any perforation of a hollow viscus and to aid in the diagnosis of a paralytic ileus. Furthermore, excretory urograms should be done in all cases of suspected urological injury and to assure the presence of normal function in the contralateral kidney. Every patient suspected of this injury should be catheterized and retrograde cystograms done when feasible. Aspiration of the space is not always a reliable means of determining the presence of a hematoma in this area.

Lastly, if the diagnosis of retroperitoneal hematoma can be made with reasonable certainty, surgery should not be performed. However, if such has been discovered during the course of an exploratory operation, simple drainage using a rubber tissue wick will be sufficient.

L. K. BEASLEY

ANTIBIOTICS IN THE PREOPERATIVE PREPARATION OF THE COLON: EVALUATION OF THE PRESENT STATUS: Robert Turell and Stanley J. Landau. J. Internat. Coll. Surgeons 31:215 (Feb.), 1959.

A critical survey is made of the value of some of the antibiotic agents currently employed for the so-called preoperative sterilization of the bowel. Neomycin and Kanamycin sulfate seem to have a similar value and action and appear to be the drugs of favor. However the benefit derived from antibiotics should be balanced against the potential reactions or risks. The advisability of the use of physiologic saline instead of tap water for bowel irrigation to prevent water intoxication and the avoidance of excessive purgation to prevent undue loss of potassium which may be responsible for postoperative hypokalemia are discussed. The problem of rapid recolonization of the patient's large intestine after so-called temporary sterilization of the colon by the normal preoperative coliform flora remains to be solved.

BERNARD J. FICARRA

SURGICAL MANAGEMENT OF DIVERTICULITIS OF THE SIGMOID COLON: S. E. O'Brien and K. I. Mustard. Canad. M. A. J. 80:257 (15 Feb.), 1959.

A series of 64 patients is presented, in whom the majority was operated upon for complications of sigmoidcolon diverticulitis. The diagnosis was often missed and some other disease suspected.

Exact statistics are given as to age, complications, operative procedures, and postoperative complications. In the latter group wound-infection and fecal fistula are frequently found.

It is the authors' conclusion, that in all cases of complications a proximal colostomy followed by a staged resection is the operation of choice. The authors concur, that in uncomplicated diverticulitis the one-stage sigmoid resection is a safe method. They express hope, that in the future this operation will be employed more frequently in order to avoid expensive and serious complications.

H. J. JOSEPH

NEGLECTED APPENDICITIS: Robert J. Freeark, Edwin Miller and Karl A. Meyer. Illinois M. J. 115:80 (Feb.), 1959.

Appendicitis is still a relatively serious disease. Because of neglect increasing morbidity and mortality, acuity in discernment is necessary to reach correct conclusions. Pain, vomiting and abdominal spasm are indications for surgery, holding good for appendicitis, perforated ulcer, intestinal obstruction, gangrenous gallbladder and other acute lesions.

In the case presented, appendiceal abscesses was noted and these should be drained extraperitoneally, after complete localization and rectally, never by abdominal incision.

Ruptured appendicitis with spreading peritonitis must be approached by open drainage and positive suction as soon as possible after diagnosis.

When in an abdominal cavity either in presence of infection or not perform surgery necessary and back out, handle contents as little as possible so as not to interfere with defensive mechanisms present or to set up new areas of tension.

J. EDWARD BROWN

LIVER AND BILIARY TRACT

ORAL METHYLTESTOSTERONE AND JAUNDICE: George L. Foss and S. Leonard Simpson. Brit. M. J. 5117:259 (31 Jan.), 1959.

Metabolism of testosterone and methyl testosterone is different. After absorption of testosterone there is increased secretion of 17-ketosteroids, but no effect on excretion of creatinine in the urine, which is not true of methyltestosterone. Patients dislike the sublingual route of testosterone as it causes unpleasant taste and sometimes nausea, thus methyltestosterone is preferred and is as effective when swallowed.

In the early years in the use of methyltestosterone, some men have found that it induces liver damage and jaundice. However, the author does not feel that this is so. In his series of 42 cases he had 2 develop liver cirrhosis and one liver metastasis and he does not attribute them to methyltestosterone.

LOUIS K. MORGANSTEIN

INDIAN CHILDHOOD CIRRHOSIS: Amarjit Singh, S. S. Jolly and M. Balasubrahmanyan. Brit. M. J. 5117:278 (31 Jan.), 1959.

All cases conformed to the criteria that infantile cirrhosis of the liver is a disease peculiar to India, affecting infants and young children, with a tendency to run in families. It is characterized by enlargement of the liver in the early stages, which is felt to be hard, also enlargement of the spleen, with ascites, with vague symptomatology, course variable, but generally rather slow and ends fatally. Etiology is unknown.

Clinical features—Acute—prognosis unfavorable, short history, negative family history. Clinical picture that of acute fulminating infectious hepatitis and most died of liver failure.

Subacute—occurs in older children and in a particular sect of Hindus with history of similar disease in the family with hepatosplenomegaly present, prognosis also grave but some recovered.

Histopathology—data is scanty, liver biopsy was done in 22 cases with 19 showing cirrhosis. There was liver degeneration, cells vacuolated, many showing eosinophils, clumping in the cytoplasm, subsequently showing structural disorganization of lobular pattern with consequent disturbances in the interlobular circulation.

LOUIS K. MORGANSTEIN

EXTRAHEPATIC COMPLICATIONS ASSOCIATED WITH CIRRHOSIS OF THE LIVER: H. Marvin Pollard, William A. Gracis, Jr. and James C. Sisson. J.A.M.A. 169:318 (24 Jan.), 1959.

The authors reviewed 201 cases of alcoholic cirrhosis of the liver. In addition to the usual complications of hepatic decompensation and portal hypertension, the occurrence of extrahepatic disease has frequently modified the management and prognosis of these patients. The authors found the following diseases associated with the alcoholic cirrhosis in their series: diabetes mellitus 19 cases, peptic ulcer 17 cases, cholelithiasis 17 cases, pancreatitis 4 cases, chronic pulmonary disease 32 cases, hypertension 14 cases, congestive heart failure 9 cases, myocardial infarction 3 cases, malignant neoplasm other than liver 12 cases, and one case of hepatoma. It seemed logical to the authors that chronic alcoholism, the altered dietary intake, and the multiple metabolic changes secondary to the hepatic disease, should affect tissues and organs

throughout the body. The above statistics certainly point out the need for thorough work-ups of every case of alcoholic hepatic cirrhosis so that associated disease may also be treated at the same time.

SAMUEL M. GILBERT

OPACIFYING GALLSTONES: Emanuel Salzman, Robert P. Spurck, Lawrence C. Kier and David H. Watkins. J.A.M.A. 169:334 (24 Jan.), 1959.

All pure cholesterol and all infectious cholesterol stones fail to opacify, and all pure pigment stones opacify as would be anticipated, according to the hypothesis that the biliverdin in the stone reacts with the contrast medium in the bile. This explains the experience and clinical observations of the opacification phenomenon by the authors. Although the chief pigment in normal human bile is bilirubin, with stasis, bilirubin in the bile is probably oxidized to biliverdin which is deposited on the surface of the bile duct stones and thereby creates the opacity. The authors describe a four-day test with the use of iopanic acid (Telepaque), using 1 gm. after each meal for four days with the patient on a relatively fat-free diet and using paregoric to control any diarrhea, as a useful method for identifying bile duct stones which opacify in over 75 per cent of cases. They feel the test is probably the best available method of demonstrating bile duct stones in the presence of jaundice, and also helpful in identifying gallbladder stones in problem cases.

SAMUEL M. GILBERT

SOME EFFECTS OF STENOSIS OF THE TERMINAL COMMON BILE DUCT ON THE BILIARY TRACT AND LIVER: John V. Pikula and J. Englebert Dunphy. New England J. Med. 260:315 (12 Feb.), 1959.

The author concludes that incomplete stricture of the lower common bile duct in dogs is associated with a rapid elevation of serum alkaline phosphatase, variable elevation of serum bilirubin, and progressive biliary cirrhosis. Gallstones occurred in 5 of 9 experiments in which an incomplete stricture without acholic stools was produced. The syndrome produced in these experiments resembles the appearance of cholangiolitic cirrhosis or primary biliary cirrhosis in man much more than the primary development of gallstones.

JACOB A. RIESE

THE SIGNIFICANCE OF THE DIRECT REACTING FRACTION OF SERUM BILIRUBIN IN HEMOLYTIC JAUNDICE: W. A. Tisdale, G. Klatskin and E. D. Kinsella. Am. J. Med. 26:214 (Feb.), 1959.

The authors report observations indicating that: 1. in hemolytic jaundice the direct reacting fraction usually constitutes less than 15 per cent of the total serum bilirubin, and rarely exceeds 1.2 mg. per cent unless there is accompanying hepatic dysfunction, 2. approximately 3 per cent of the unconjugated bilirubin in the serum is capable of diazotizing in the absence of alcohol within one minute, and hence accounts for a variable fraction of the direct reacting pigment depending on the concentration of unconjugated bilirubin present, 3. the direct reacting fraction present in excess of 3 per cent of the total serum bilirubin probably represents bilirubin glucuronide regurgitated from the bile, 4. such regurgitation occurs in the normal liver when the excretion of bilirubin glucuronide is greatly accelerated by excessive hemolysis or the infusion of large amounts of unconjugated bilirubin, and is enhanced when hepatic disease is a complication, 5. the fraction of direct reacting pigment found in the serum under these circumstances is more closely correlated with the amount of bilirubin excreted in the bile than with its concentration in the serum, and hence tends to be very low in conditions such as uncomplicated erythroblastosis fetalis, in which conjugation and excretion are subnormal, and 6. bilirubinuria is seen occasionally in uncomplicated hemolytic jaundice, but is a regular finding in normal subjects infused with large amounts of crystalline bilirubin.

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1. Nesselrod, J. P.: Clinical Proctology, ed. 2, Philadelphia, Saunders, 1957. 2. Page, S. G., Jr., et al.: J. A. M. A. 157:1208, Apr. 2, 1955. 3. Gross, J. M.: J. Internat. Coll. Surgeons 23:34, Jan., 1955. 4. Page, S. G., Jr., et al.: Gastroenterology 32:747, Apr., 1957. 5. Hellman, L. D.: To be published.

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*Archambault, R.: Canad. M. A. J. *81*:28, 1959.

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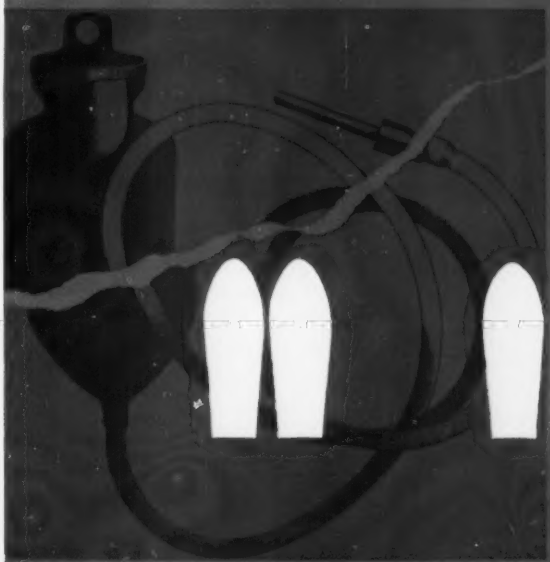

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DU 6-60

Even where all other agents have failed – Sorboquel arrests long-standing, uncontrolled, exhausting diarrheas

Unexcelled Therapeutic Response: Results of the Administration of Sorboquel Tablets[1-3]

	No. of Patients	*Response*		
		Excellent	*Good*	*Poor*
Chronic Diarrhea*	**485**	335	76	74
		84.7%		15.3%
Acute Diarrhea**	**332**	288	22	22
		93.4%		6.6%

*Chronic diarrheas include irritable bowel syndrome, regional enteritis, diverticulitis and ulcerative colitis, postantibiotic enteritis, malabsorption syndrome, radiation proctitis, surgically short-circuited intestinal states. Diarrhea had persisted for more than a year in a large percentage with bowel movement frequency averaging from 5 to more than 10 a day. In most patients, SORBOQUEL controlled the condition within 3 days, even where other agents had failed.

**Acute diarrheas include nonspecific gastroenteritis, enteritis, enterocolitis. Control of the diarrhea was achieved within 24 hours in most cases.

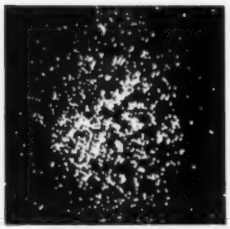
Dual-action **Sorboquel** arrests diarrhea even where all other agents have failed

The components in Sorboquel: the culmination of many years of development

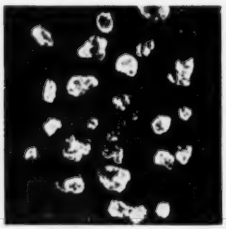
SORBOQUEL Tablets combine two unique and hitherto unavailable antidiarrheal agents—polycarbophil and thihexinol methylbromide. Acting together, through different but complementary mechanisms, these components in SORBOQUEL *absorb* free fecal water and *quell* hypermotility and associated spasm to an exceptional degree.

For too fluid feces, an extraordinary ability to absorb free fecal water

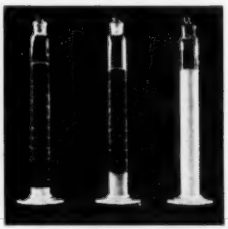
(through the hydrosorptive action of new polycarbophil)



Dry State
Demonstration of the particulate nature of dry polycarbophil.



Swollen State
Note the particulate nature of swollen polycarbophil. Impaction is virtually impossible.



(a) (b) (c)

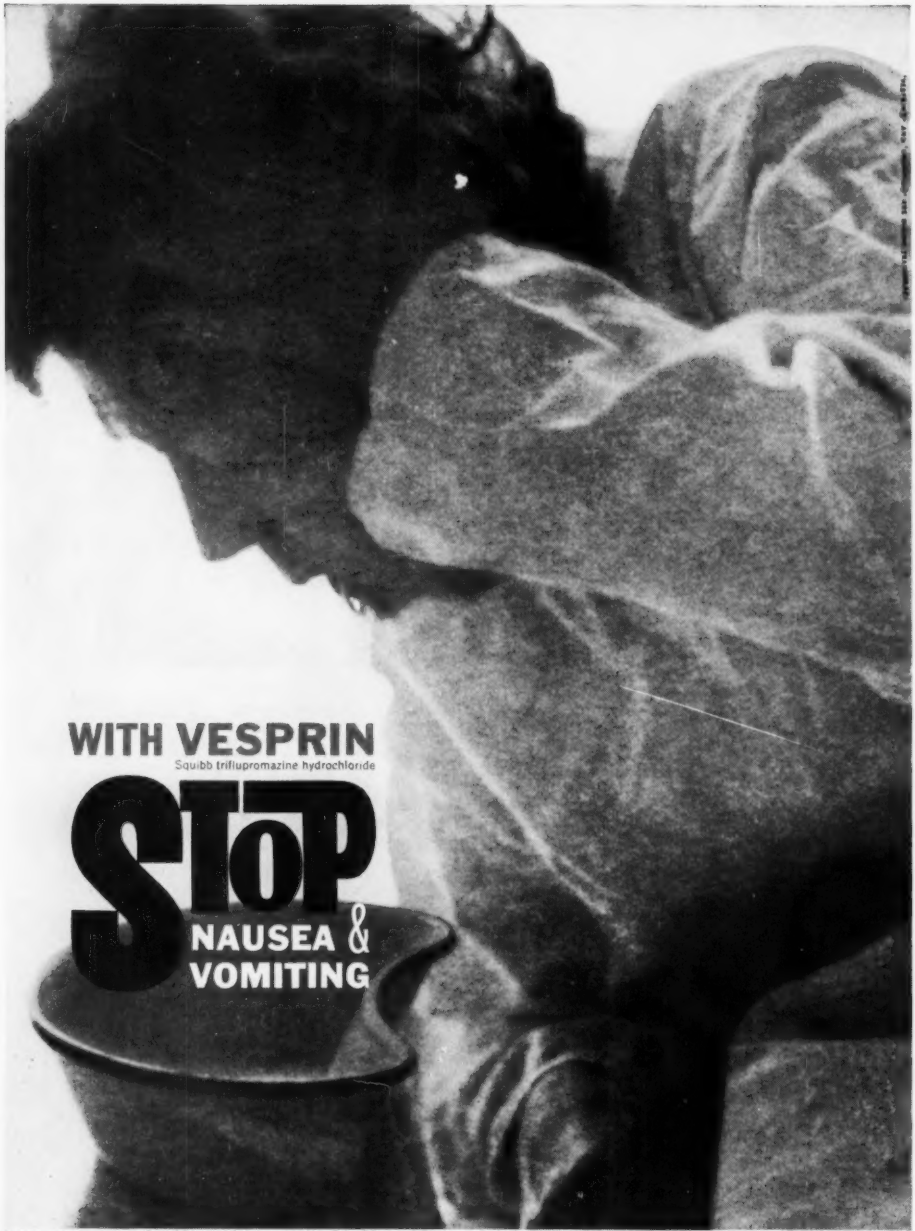
Demonstration of the dependence of swelling of polycarbophil on pH (a) pH of stomach; (b) pH of duodenum; (c) pH of intestines.

A newly synthesized macromolecular substance exhibiting extraordinary capacity for absorption and retention of free fecal water[9-11] ■ the colloidal suspension is free-flowing, since, in the swollen or hydrated state, the particulate structure is retained[9] ■ exerts marked hydrosorptive action only on reaching the alkaline medium of the small intestine and colon ■ virtually free of impaction qualities ■ pharmacologically inert, not absorbed from the gut[12]

Convenient tablet form; simple, uncomplicated dosage schedule

SORBOQUEL DOSAGE: For older children and adults, initial dosage of one SORBOQUEL Tablet q.i.d. is usually adequate. Severe diarrheas may require six, or even eight, tablets in divided daily doses. (Dosages exceeding six tablets a day should not be employed over prolonged periods.) Many patients can be maintained on one to three tablets daily after the diarrhea is brought under control.

SIDE EFFECTS: The incidence of side effects at recommended dosage is negligible. (The usual precautions when using parasympatholytic agents should be observed. *Complete information regarding the use of* SORBOQUEL TABLETS *is available on request.*



Dosage: Intravenous, 5 to 12 mg. / Intramuscular, 5 to 15 mg. / Oral prophylaxis, 20 to 30 mg. daily / **Supply:** Tablets, 10, 25, and 50 mg., bottles of 50 and 500 / Emulsion, 30-cc. dropper bottles and 120-cc. bottles (10 mg./cc.) / Parenteral Solution, 1-cc. multiple dose vial (20 mg./cc.) / 10-cc. multiple dose vial (10 mg./cc.) / Vesprin Injection Unimatic (15 mg. in 0.75 cc.)

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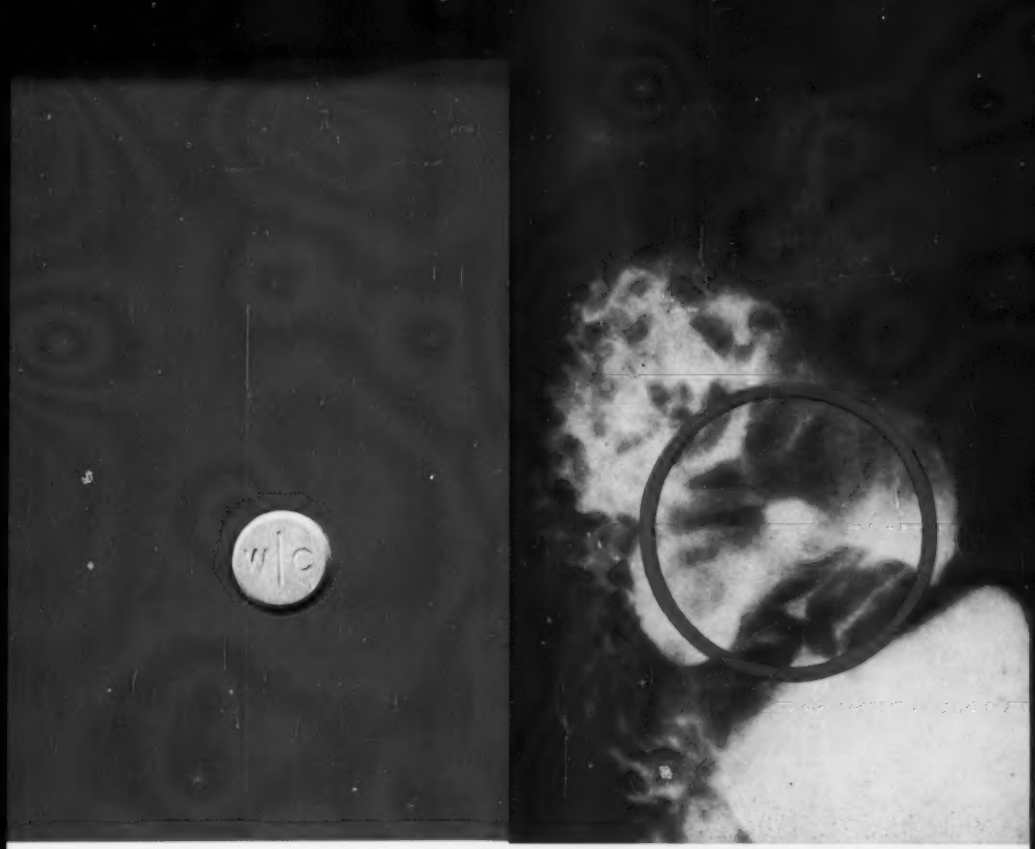

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1. Wharton, G. K. and Osmon, K. L.; Antacid Therapy in Peptic Ulcer: Clin. Med. V·5 (May, 1958).
2. McHardy, G. et al; Exhibit, So. Med. Assn., New Orleans, La., Nov. 1959.

*Full-color photographs with explanatory text of recent photogastroscopy have been mailed to you.

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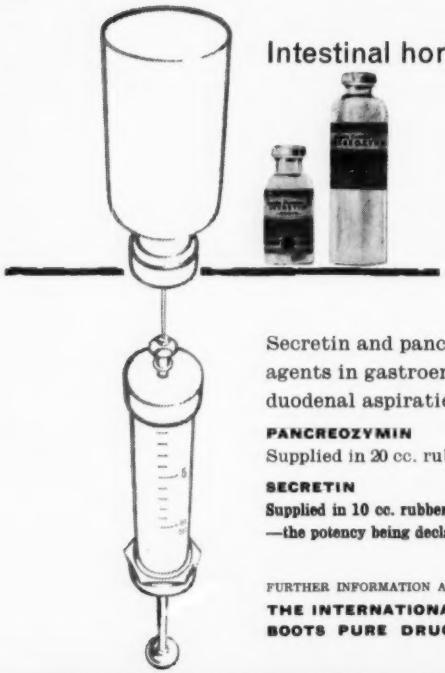

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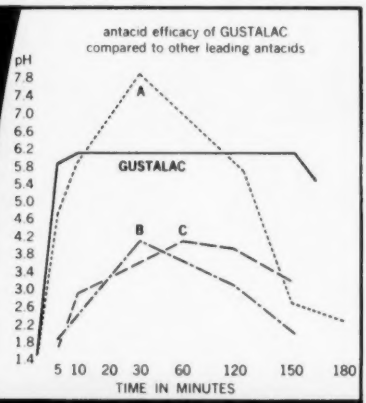

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1. Kirstner, J. B.: J.A.M.A. 166:1727, 1958.

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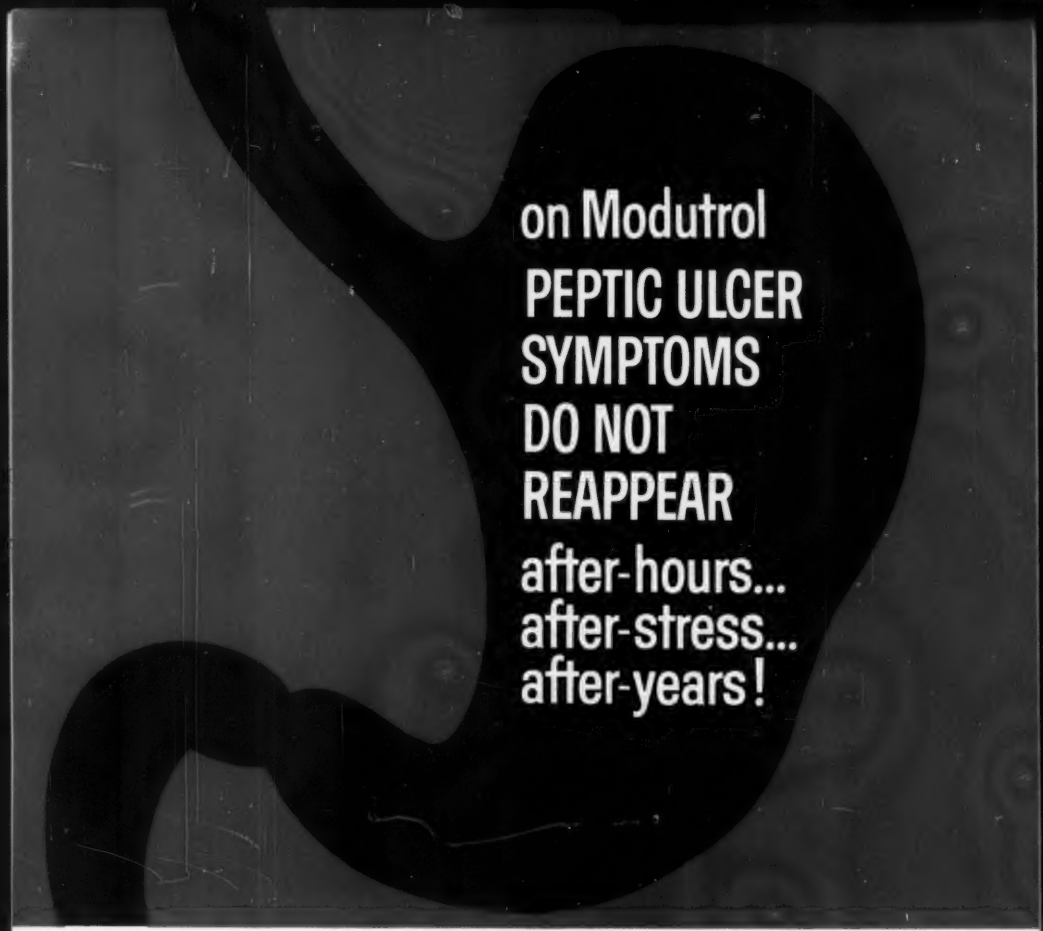

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1. Rosenblum, L. A.: Report, Symposium on Peptic Ulcer, University of Vermont School of Medicine, September 24, 1959.

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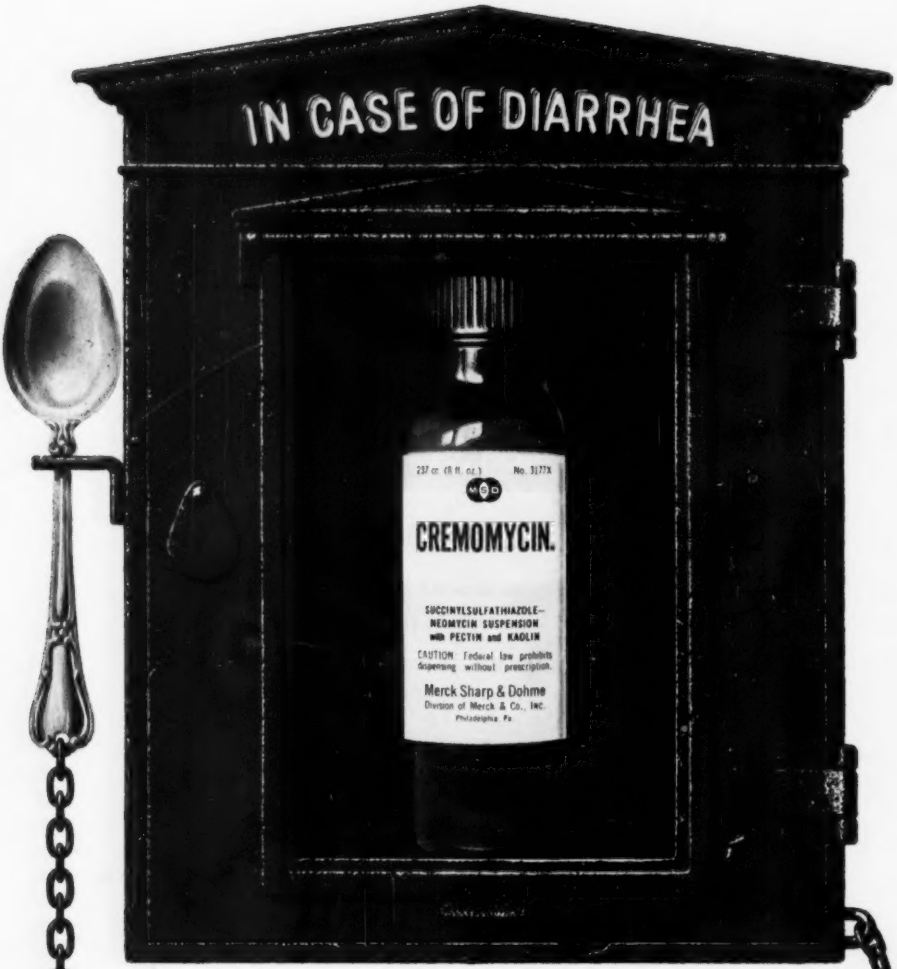

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